

CELL ADAPTATIONS

CELL INJURY

CELL DEATH

DR. PRIYANKA SACHDEV , MD

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Cell Adaptation & Injury*



*Scan or Click to watch
Apoptosis & Necrosis*



*Scan or Click to watch
Inflammation*



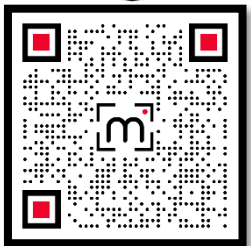
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Haemodynamic Disorder*



TYPES OF CELLS

1. Labile cells
2. Stable cells
3. Permanent cells

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Labile

Continuous regeneration from stem cells (self-renewal)

- a) Hematopoietic cells in bone marrow
- b) Surface epithelia – skin, oral cavity, vagina, cervix
- c) Duct epithelia – salivary glands, pancreas, biliary tract
- d) Mucosas – GIT, uterus, fallopian tubes, urinary bladder

Stable

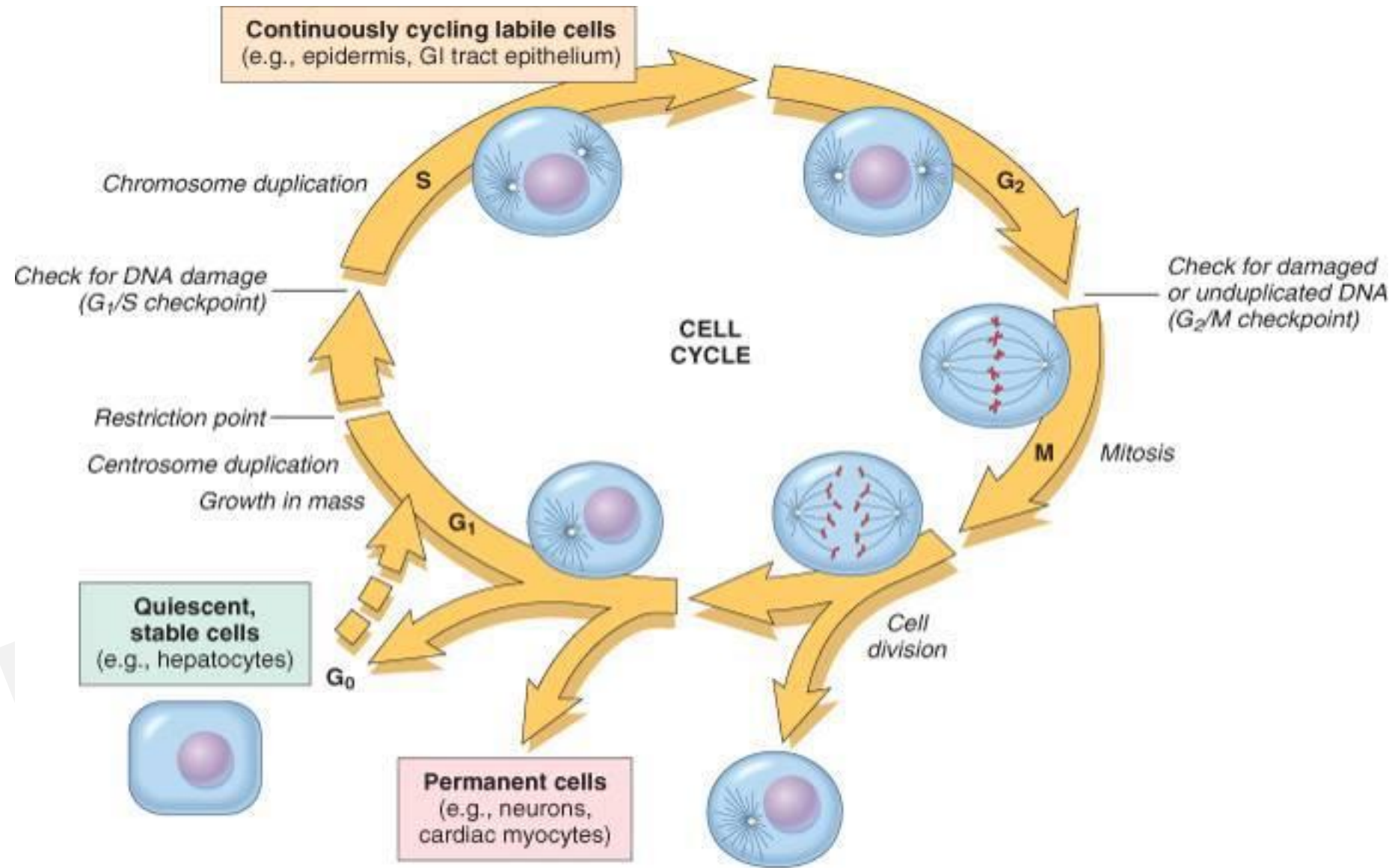
Regeneration as response to injury

- a) Parenchyma – liver, pancreas, renal tubules
- b) Mesenchymal cells, endothelium

Permanent

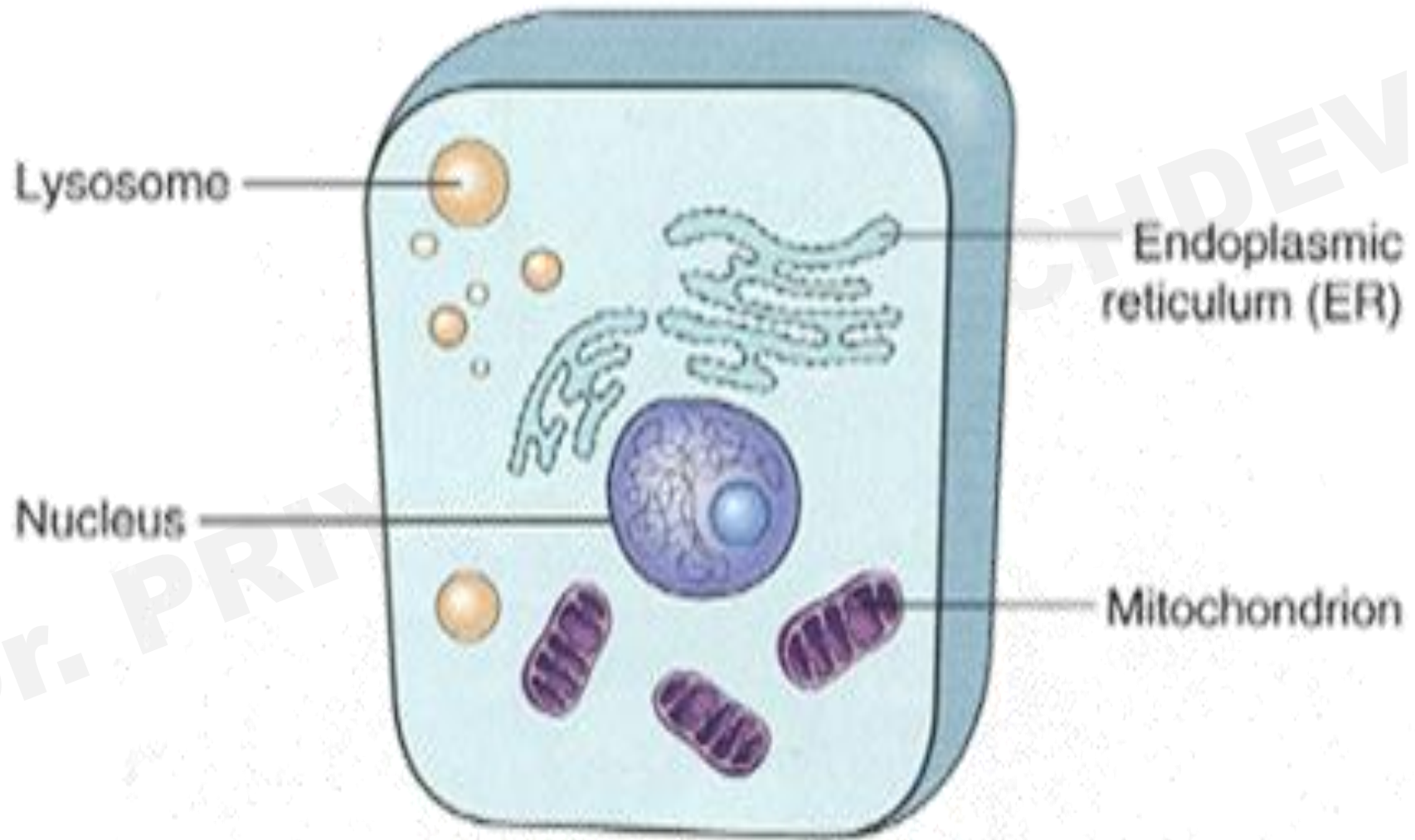
Nonproliferative in postnatal life

- a) Neurons
- b) Cardiomyocytes



INTRODUCTION

- **Cells** are the **structural and functional units** of tissues and organs.
- Normal cells have a fairly narrow range of function or steady state: **Homeostasis**



A. Normal cell

Normally cells in homeostasis



Physiological and pathological stress



Cellular adaptation (reversible on withdrawal of stimulus)



If the irritant stimulus persists for long time



Cell injury



Reversible cell injury

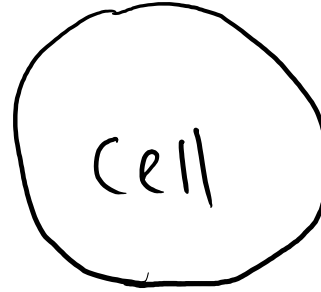


Irreversible cell injury (Cell death)

-Apoptosis

-Necrosis

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Cell Adaptation & Injury*



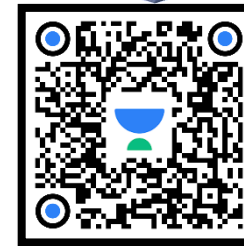
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Apoptosis & Necrosis*

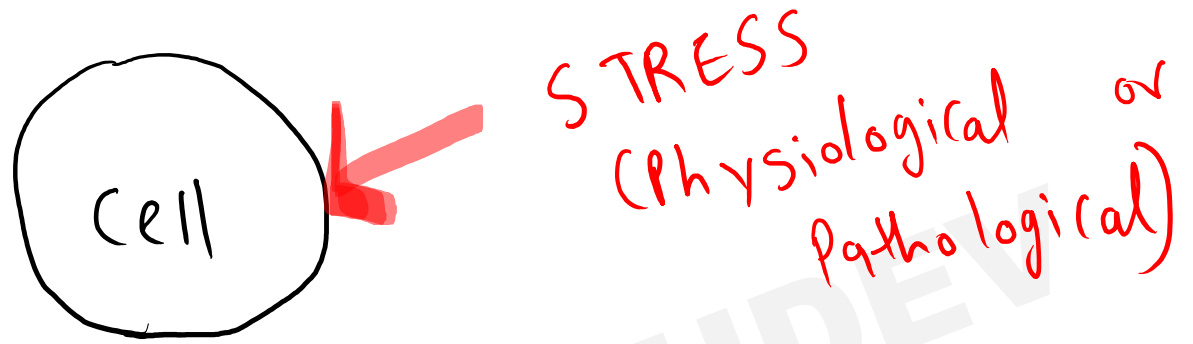


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Inflammation*



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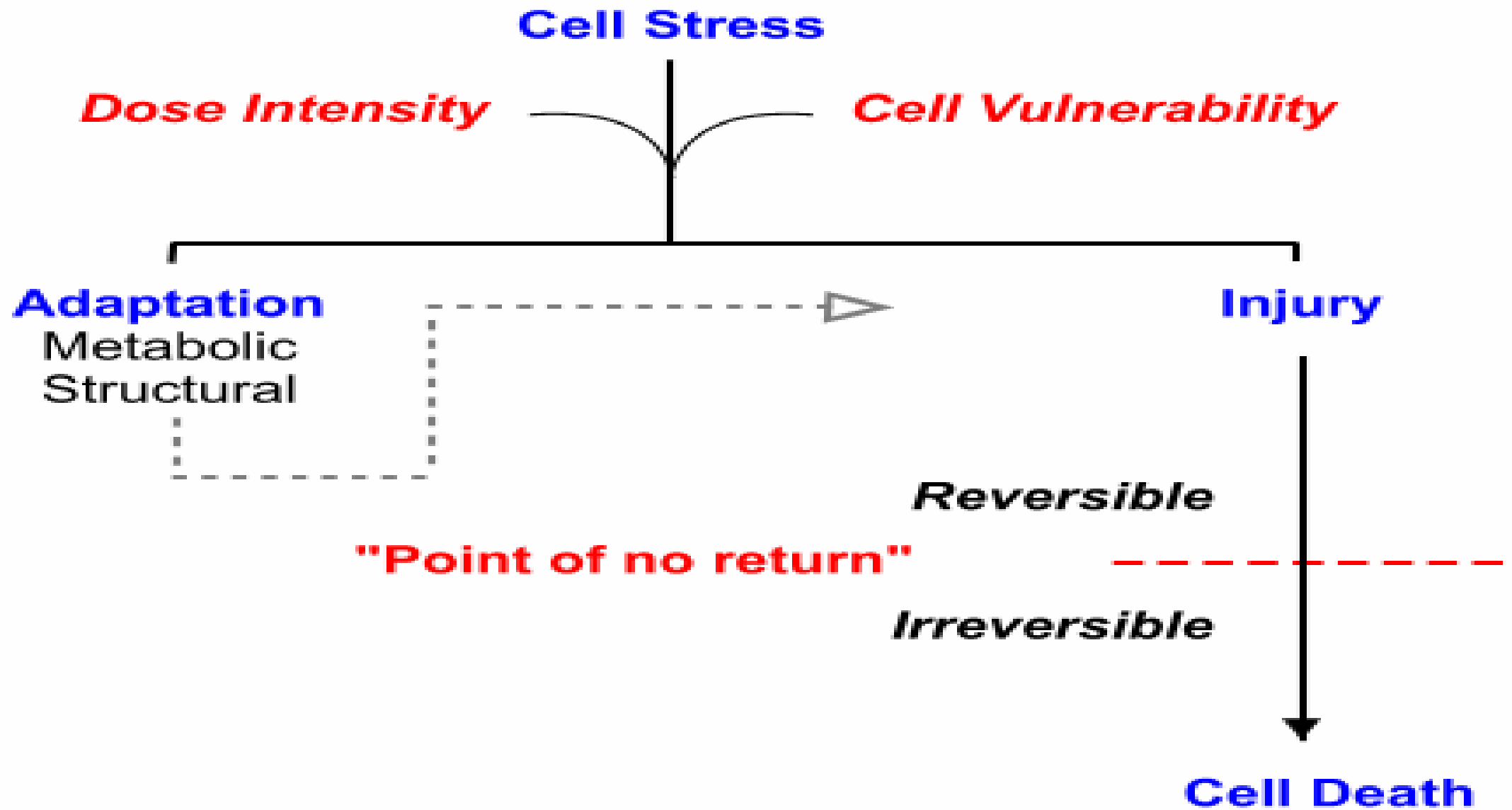




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- **Cell injury** results when cells are stressed so severely that they are **no longer able to adapt**
- i.e., when the limits of adaptive response to a stimulus are exceeded, cell injury occurs.

- Cell injury is reversible up to a certain point, but if the stimulus persists or is severe enough from the beginning, the cell reaches a **“point of no return”** and suffers irreversible injury and ultimate cell death.

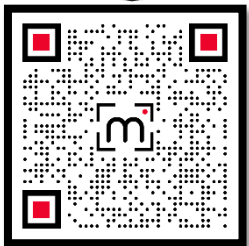


- **Adaptation, reversible injury and irreversible injury & cell death** are stages of progressive impairment of the cell's normal function and structure.

CELL DEATH

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CELL DEATH

- Apoptosis
- Necrosis

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Apoptosis

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Apoptosis & Necrosis*



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Inflammation*



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Haemodynamic Disorder*



OVERVIEW

- **Definition**
- **Types**
- **Mechanisms**
- **Morphological changes in apoptosis**
- **Diagnosis of Apoptosis**
- **Differences from necrosis**

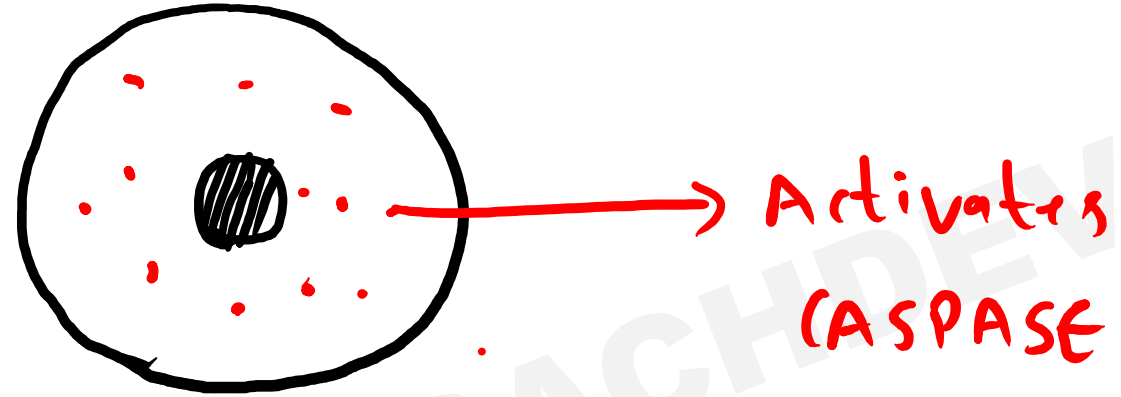
Definition

CELL SUICIDE

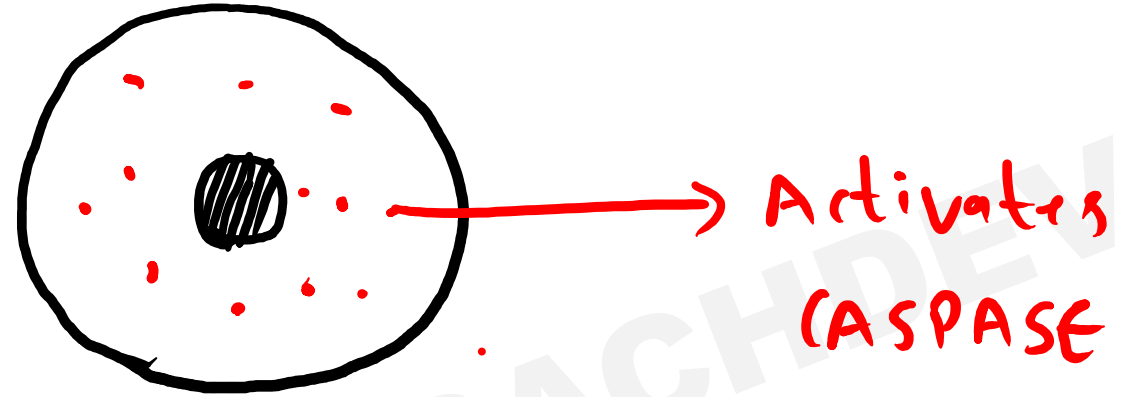
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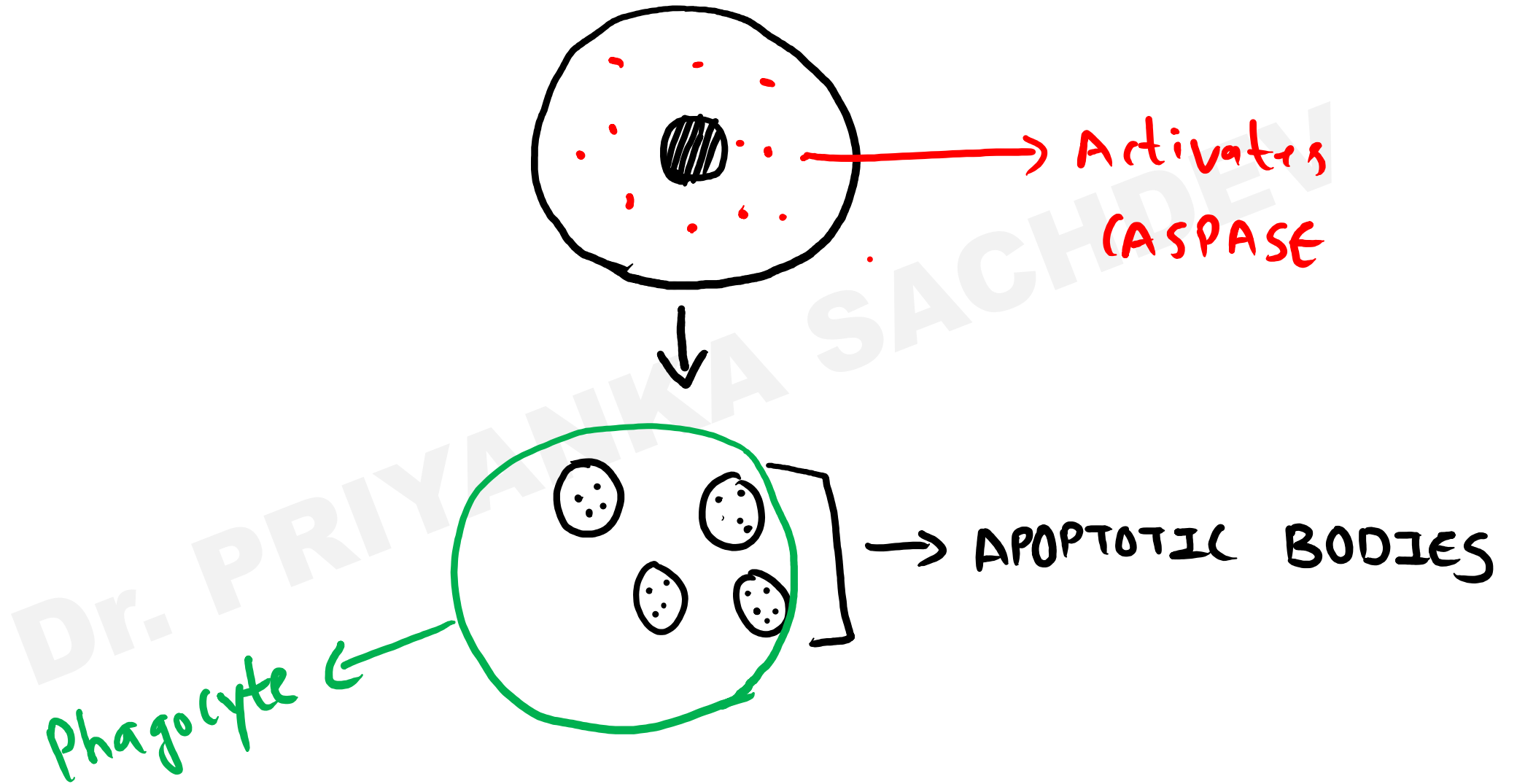
Definition

- It is a pathway of **cell death** that is induced by a **tightly regulated intracellular program** in which cells destined to die activate enzymes (**caspase**) degrade the cells own nuclear DNA and cytoplasmic proteins.
- The cell is phagocytosed
- There is no leakage outside
- So there is no inflammation



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Definition

- It is a pathway of **cell death** that is induced by a **tightly regulated intracellular program** in which cells destined to die activate enzymes (**caspase**) degrade the cells own nuclear DNA and cytoplasmic proteins.
- The cell is phagocytosed
- There is no leakage outside
- So there is no inflammation

- It is the **way of elimination** of unwanted cells and those cells which are damaged beyond repair capacity of cell.

- Apoptosis generally involves **single cell** in contrast to necrosis that usually involve a group of cells.

- It is the ‘ **programmed cell death**’.
- It is **genetically programmed**.
- It is an **energy dependent** process.

POLLS 1

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Apoptosis & Necrosis*



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Inflammation*



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Central to apoptosis is the utilization of

- **a) Nitrous oxide**
- **b) Adenyl cyclase**
- **c) Caspases**
- **d) c-AMP**

Central to apoptosis is the utilization of -

- a) Nitrous oxide
- b) Adenyl cyclase
- c) Caspases
- d) c-AMP

OVERVIEW

- **Definition**
- **Types**
- **Mechanisms**
- **Morphological changes in apoptosis**
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- **Differences from necrosis**

TYPES

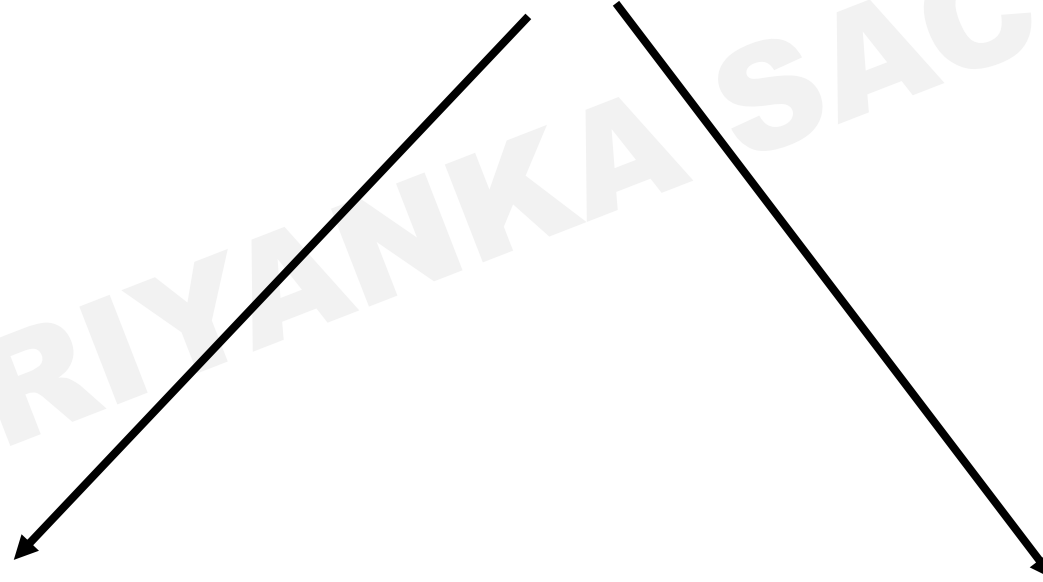
Apoptosis may be of two types →

- **A) Physiological** → Programmed cell death
- **B) Pathological** → Unprogrammed cell death

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APOPTOSIS



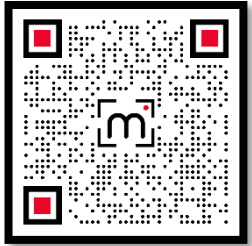
Physiological

Pathological

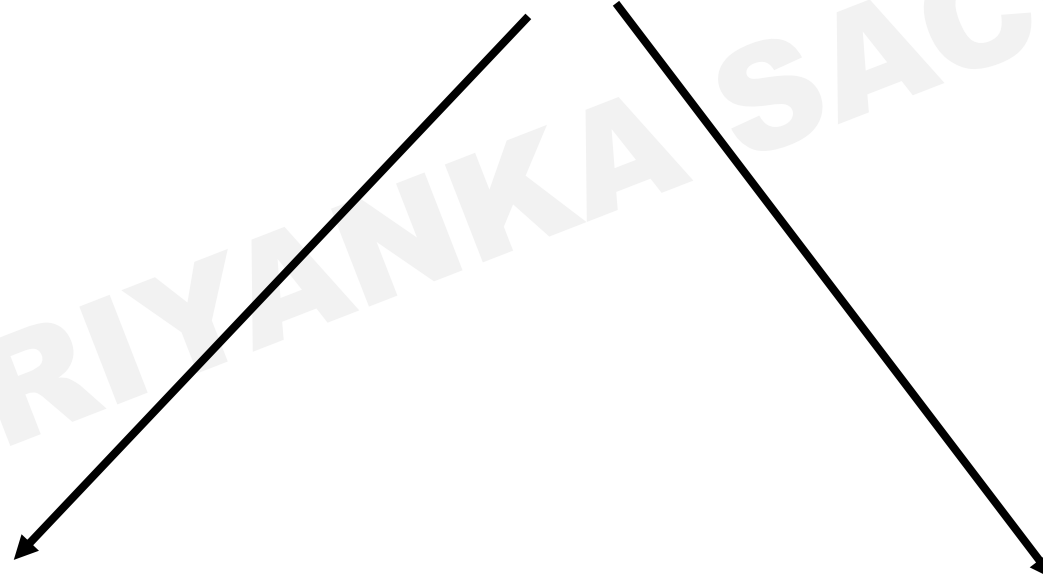
Physiological causes

1. Embryogenesis
2. Elimination of potentially self reacting lymphocytes.
3. Hormone dependent involution of uterus and breast.
4. Death of cells that have completed their functions

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APOPTOSIS



Physiological

Pathological

Pathological Causes

- 1. Cell death in tumours exposed to chemotherapeutic agents.
- 2. Progressive depletion of CD4+T cells in the pathogenesis of AIDS.
- 3. Cell death in viral infections e.g. formation of Councilman bodies in viral hepatitis.

OVERVIEW

- **Definition**
- **Types**
- **Mechanisms**
- **Morphological changes in apoptosis**
- **Diagnosis of Apoptosis**
- **Differences from necrosis**

Mechanism

- Apoptosis can be induced through two distinct but convergent pathways.

1. **Extrinsic pathway** – it is initiated by extracellular stimulus with help of specific receptors called **death receptors**
2. **Intrinsic pathway** – it is result of increased **mitochondrial membrane** permeability and release of pro- apoptotic markers like cytochrome C into the cytoplasm.

Mechanism

```
graph TD; Mechanism --> Extrinsic[Extrinsic pathway]; Mechanism --> Intrinsic[Intrinsic pathway]; Extrinsic --> Initiation1[Initiation]; Extrinsic --> Execution1[Execution]; Intrinsic --> Initiation2[Initiation]; Intrinsic --> Execution2[Execution];
```

Extrinsic pathway

Intrinsic pathway

Initiation

Execution

Initiation

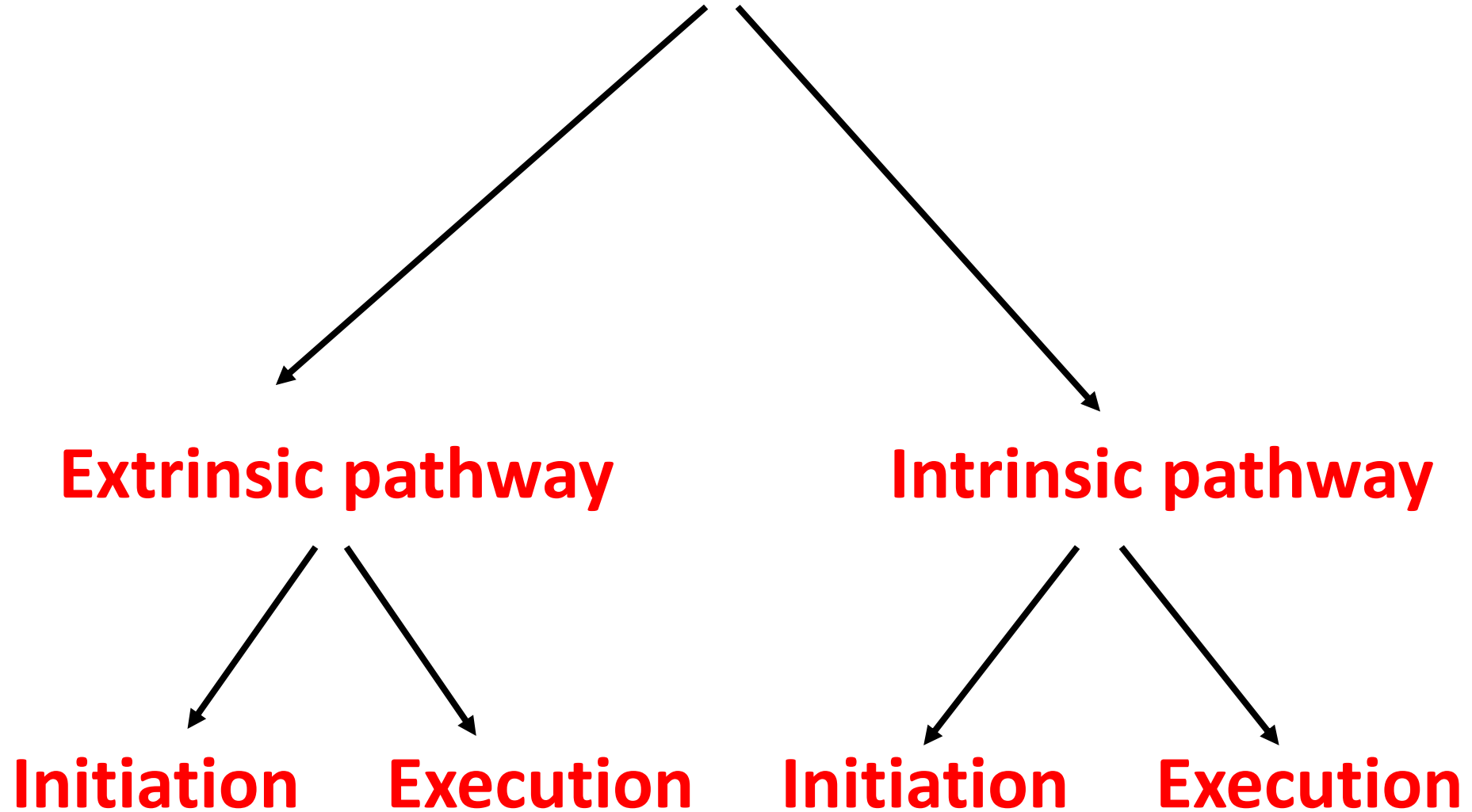
Execution

Phases

Apoptosis can be divided into two phases:

- 1. Initiation phase** : starts with stimulus (either extrinsic or intrinsic) and consist of catabolic activation of caspase like 8 or 9.
- 2. Execution phase**: executioner caspases act to cause cell death.

Mechanism

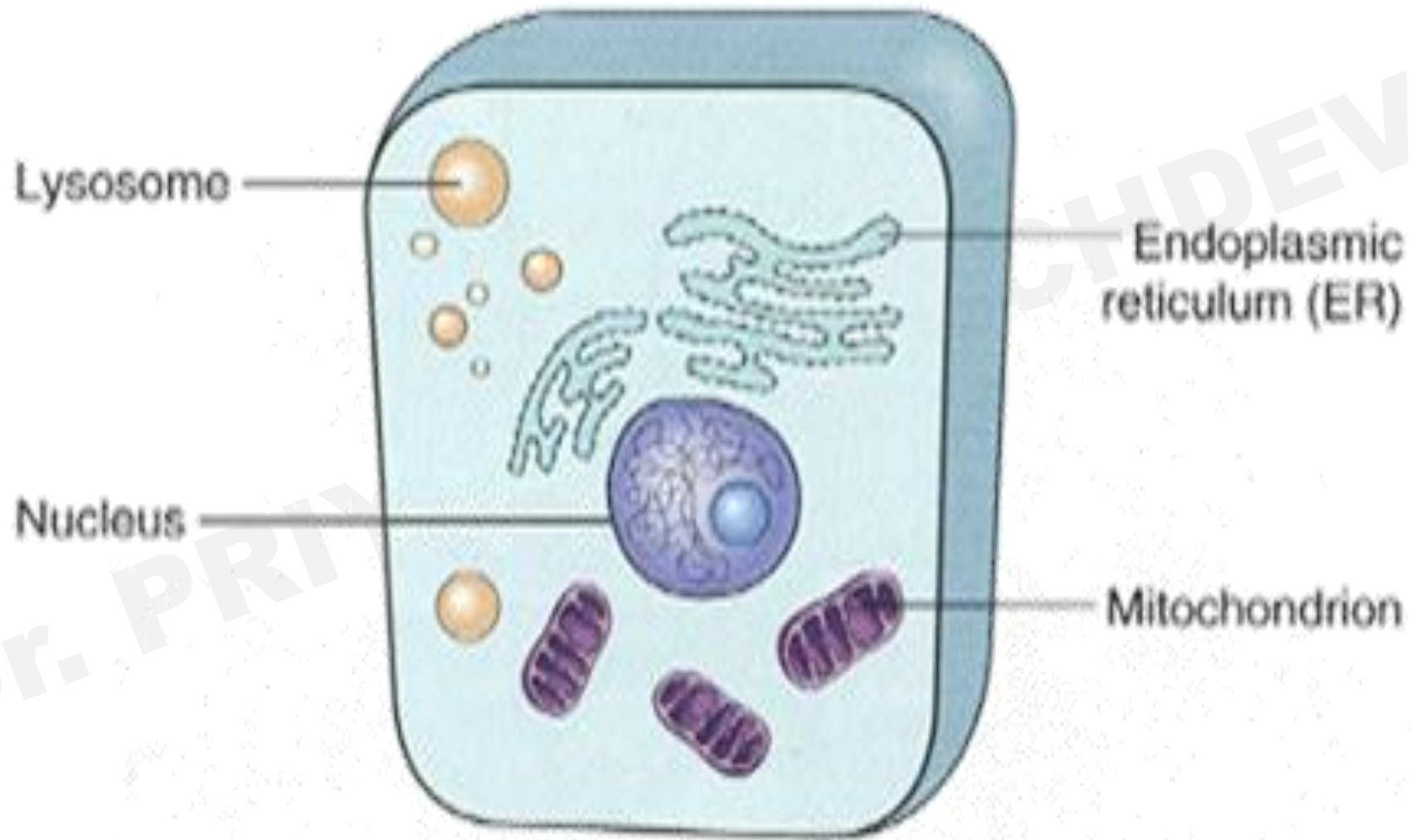


Extrinsic pathway → Initiation phase

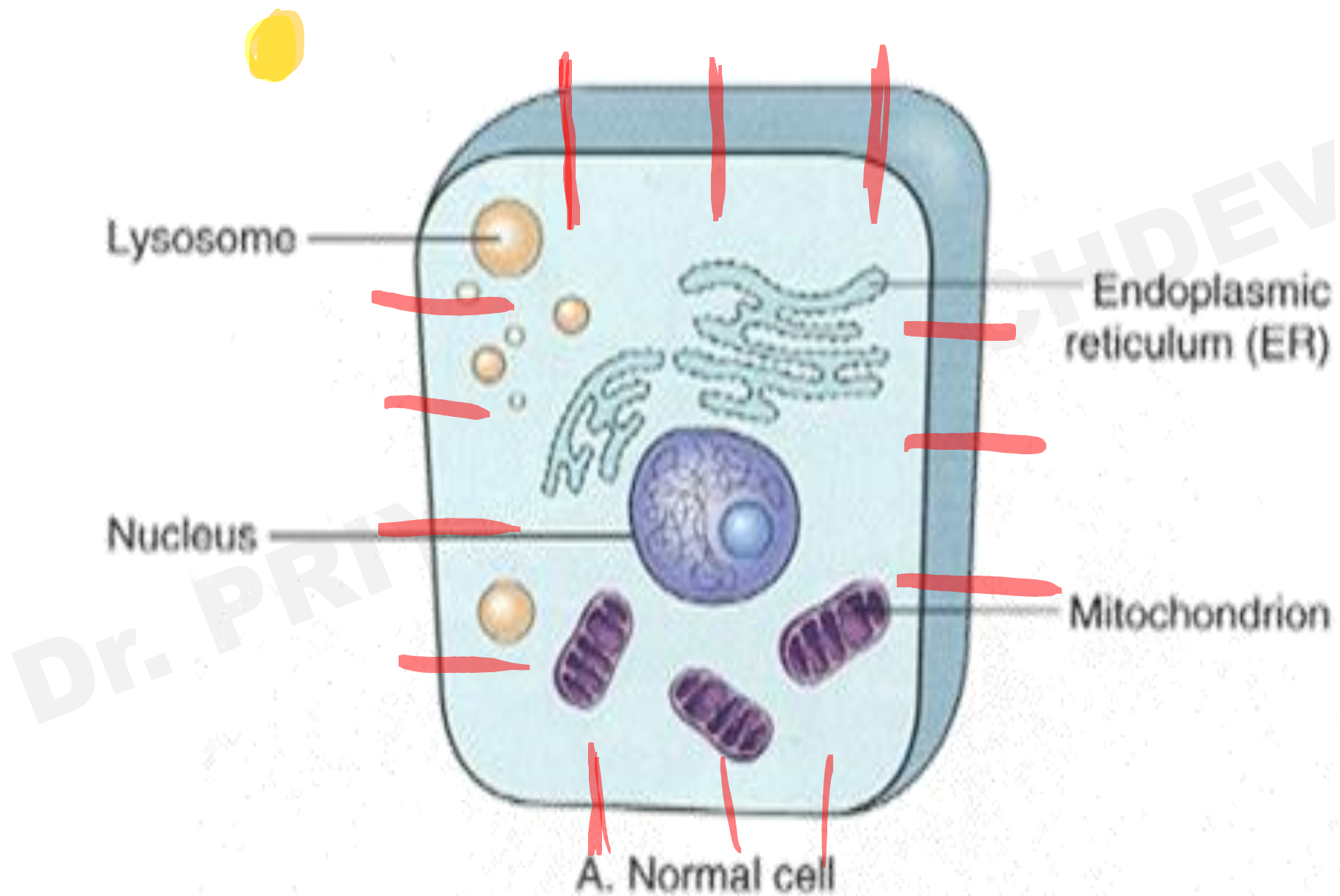
- It is initiated through specific receptors called **death receptors**

1. Fas protein (CD95)

2. TNF receptors



A. Normal cell



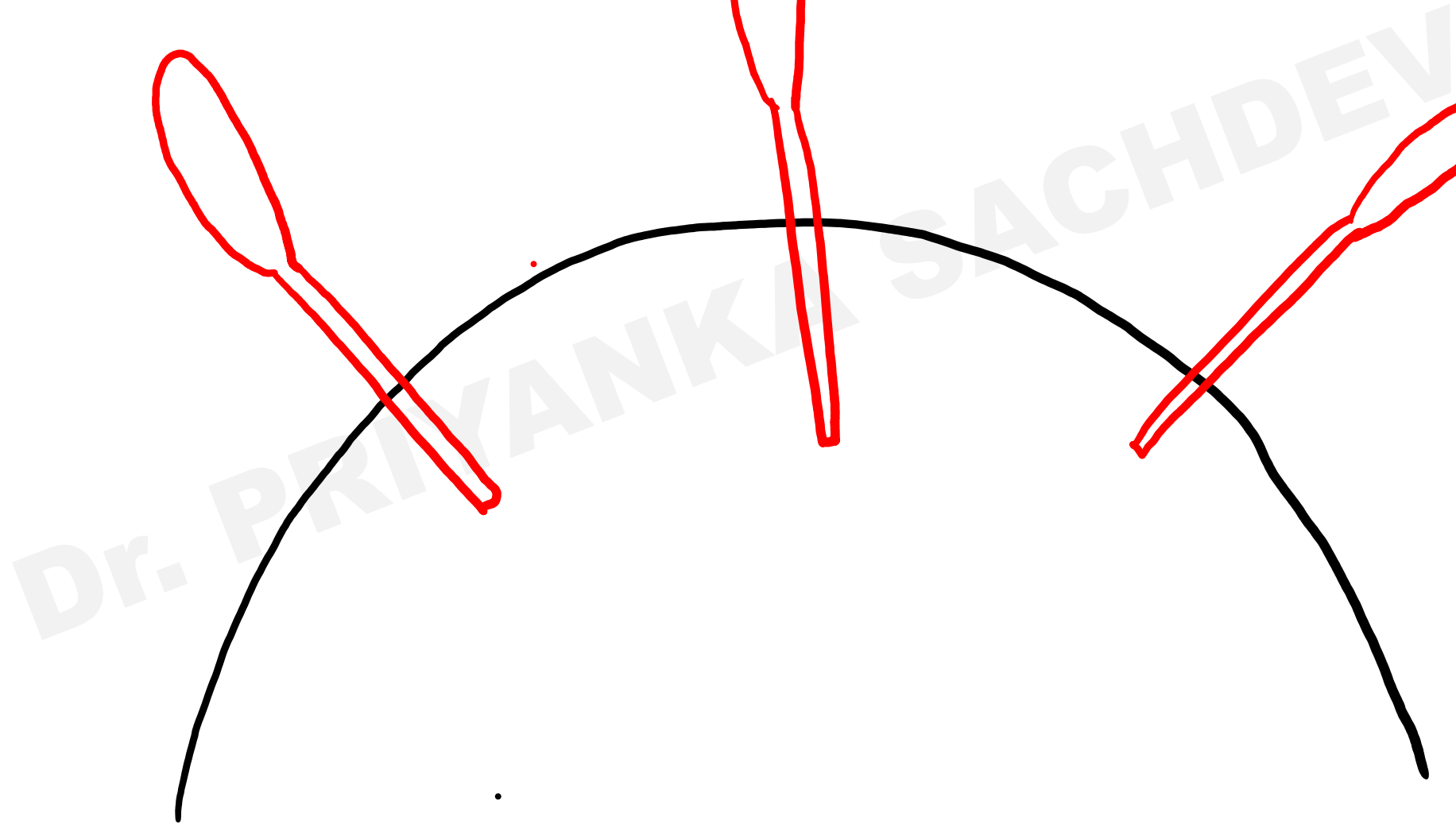

FAS (CD95)
Ligand

→ Death receptors
(FAS/CD95 receptor)

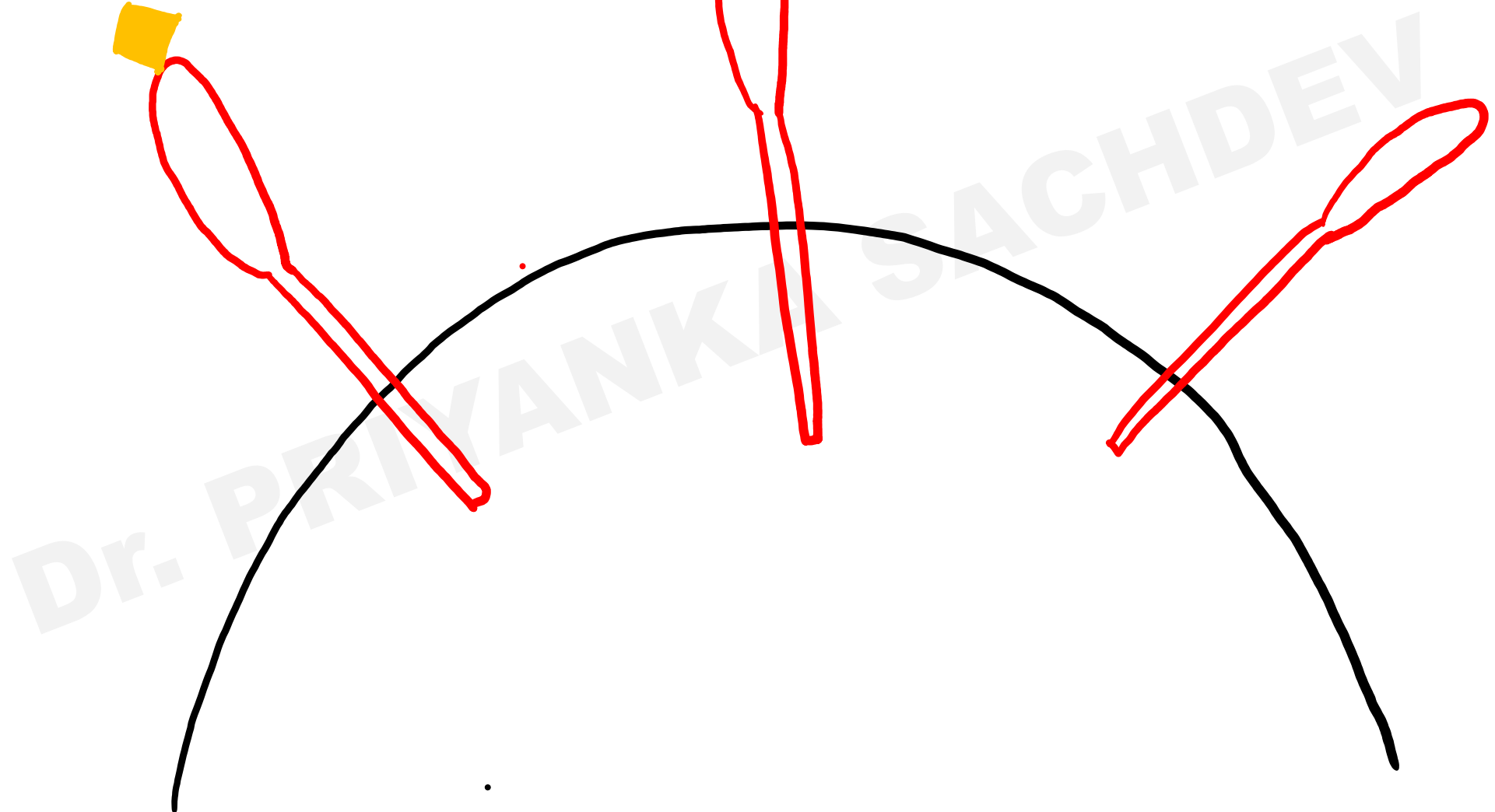
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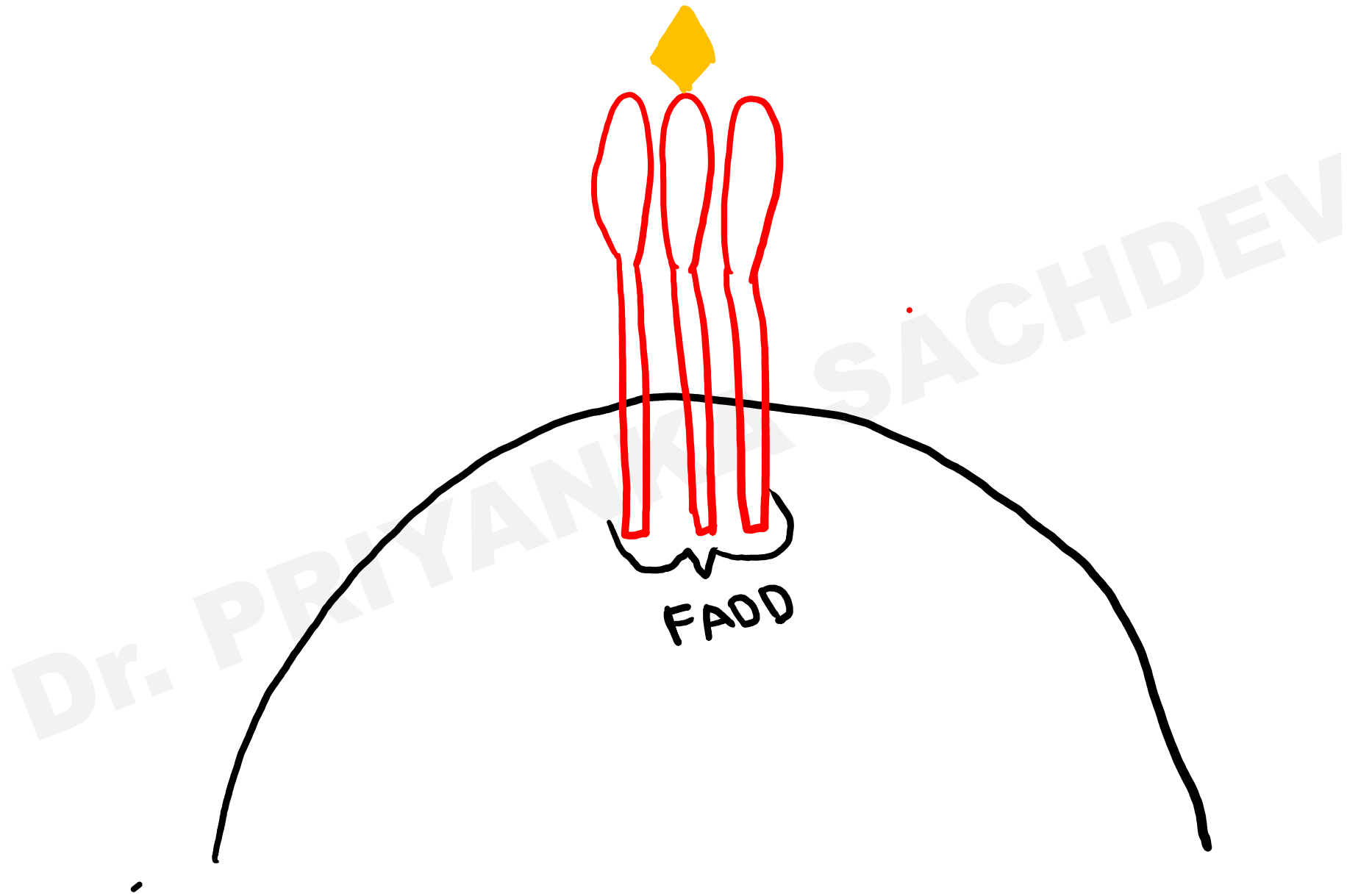
 FAS (CD 95)

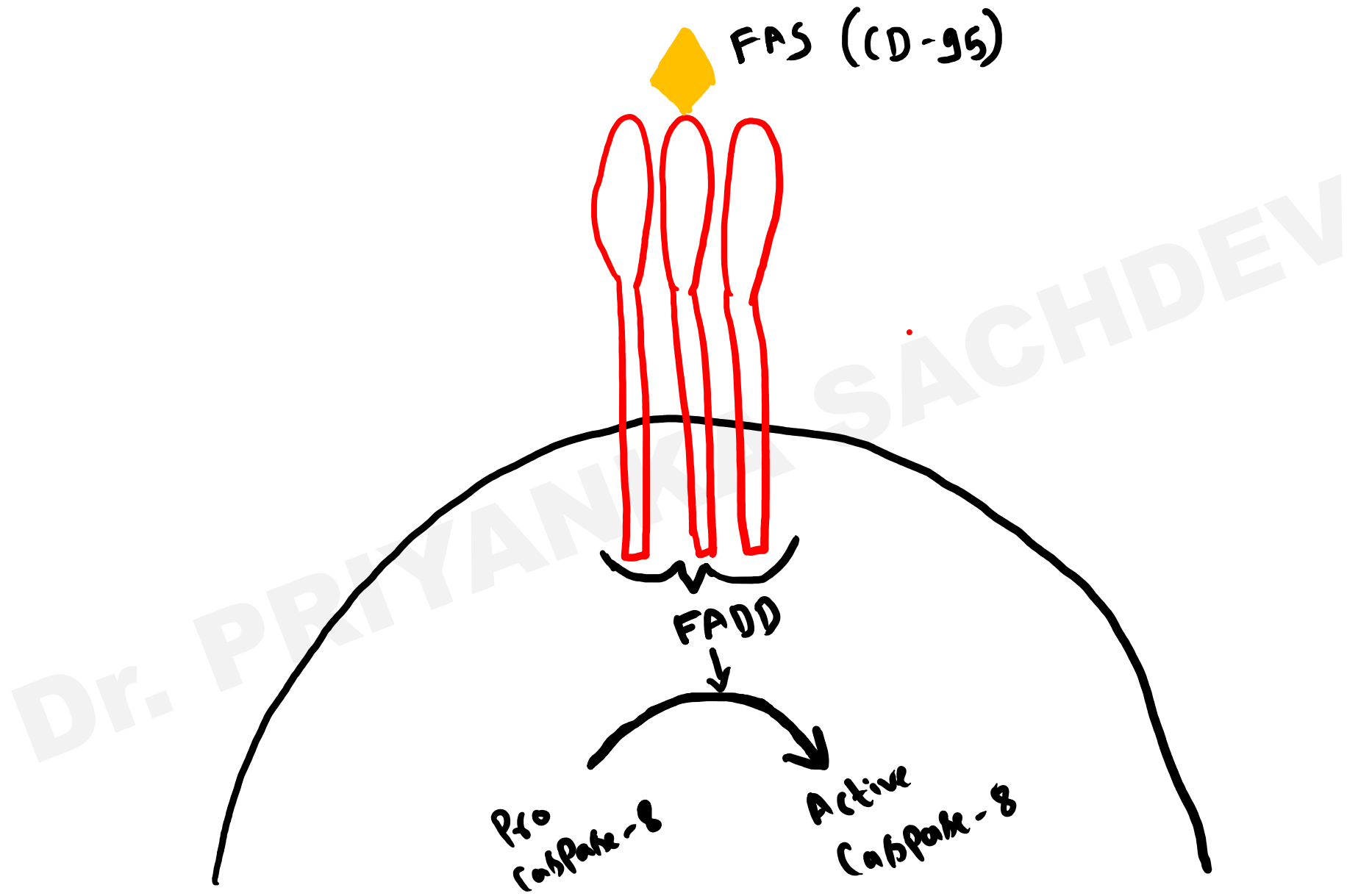
→ Death receptors
(FAS / CD 95 receptor)

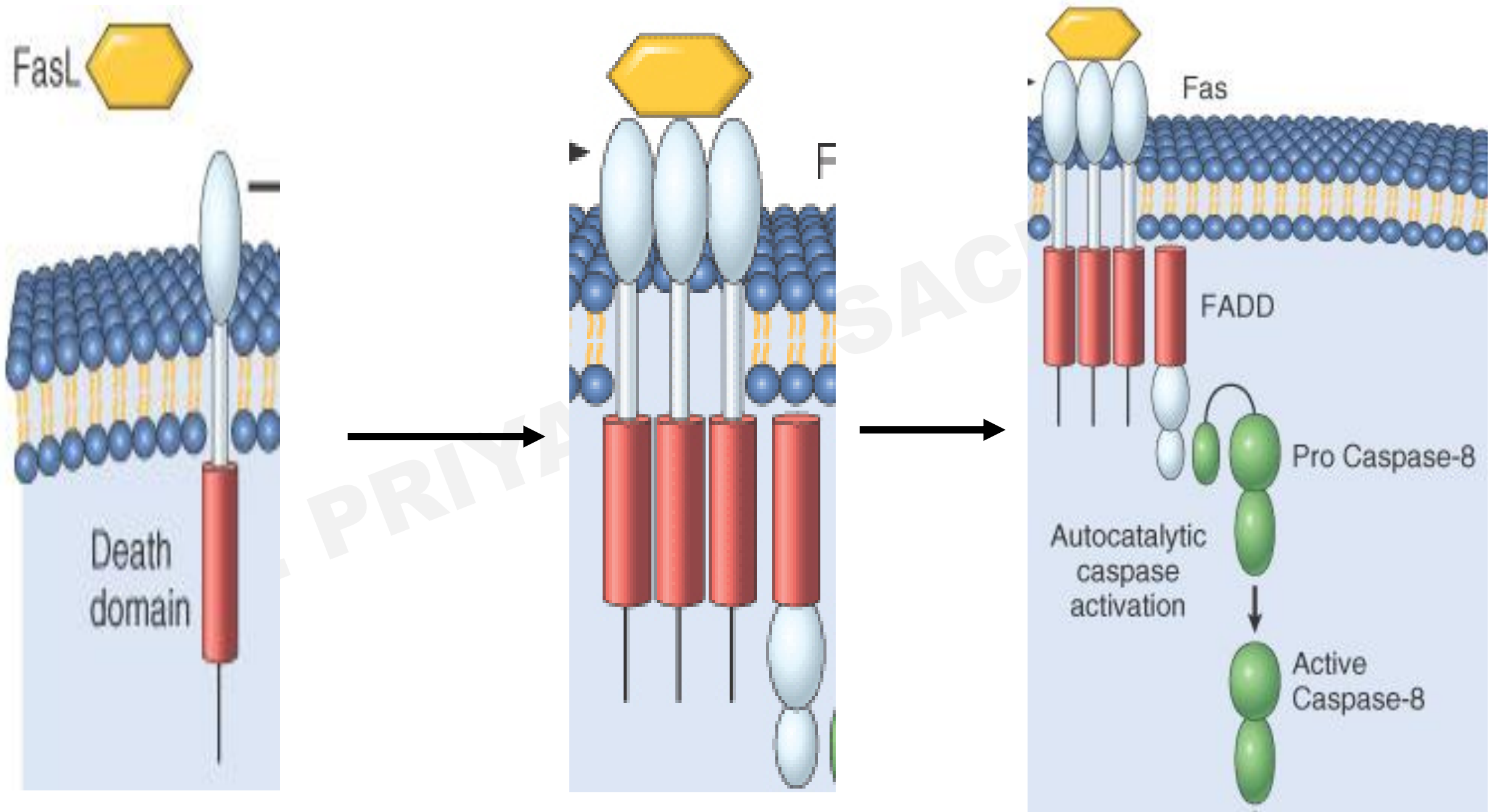


FAS (CD 95)









Fas protein (CD95)



Fas receptor (Death receptor)



Multiple Fas proteins come together



Cytoplasmic death domains combine to form a death domain

FADD



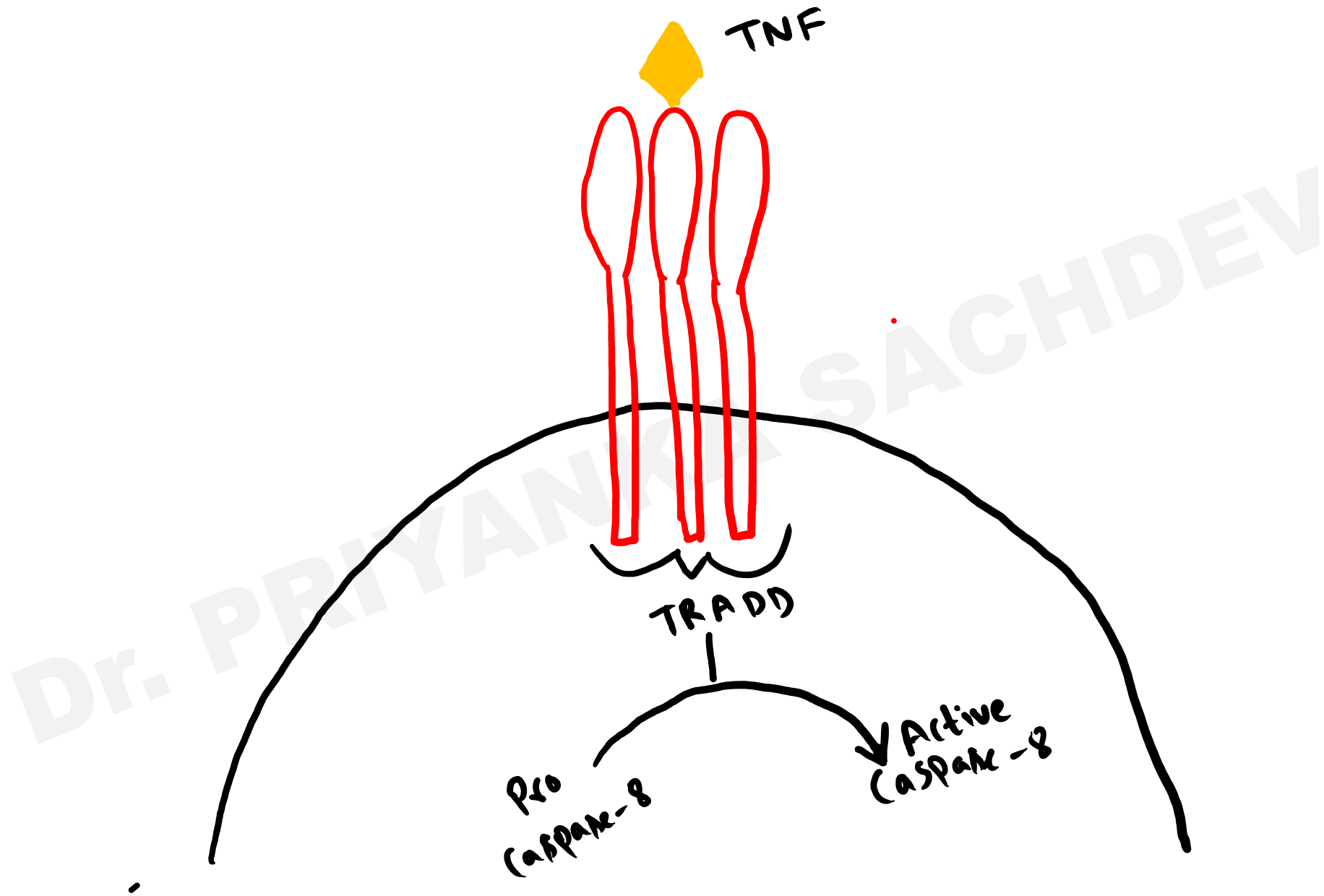
Activate pro- caspsase 8 to active caspase 8

Extrinsic pathway → Initiation phase

- It is initiated through specific receptors called **death receptors**

1. Fas protein (CD95)

2. TNF receptors



TNF



TNF receptor



Multiple Fas proteins come together



Cytoplasmic death domains combine to form a death domain

TRADD



Active pro- caspsase 8 to active caspase 8

Mechanism

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graph TD; Mechanism --> Extrinsic[Extrinsic pathway]; Mechanism --> Intrinsic[Intrinsic pathway]; Extrinsic --> Initiation1[Initiation]; Extrinsic --> Execution1[Execution]; Intrinsic --> Initiation2[Initiation]; Intrinsic --> Execution2[Execution];
```

Extrinsic pathway

Intrinsic pathway

Initiation

Execution

Initiation

Execution

Mechanism

Extrinsic pathway

Intrinsic pathway

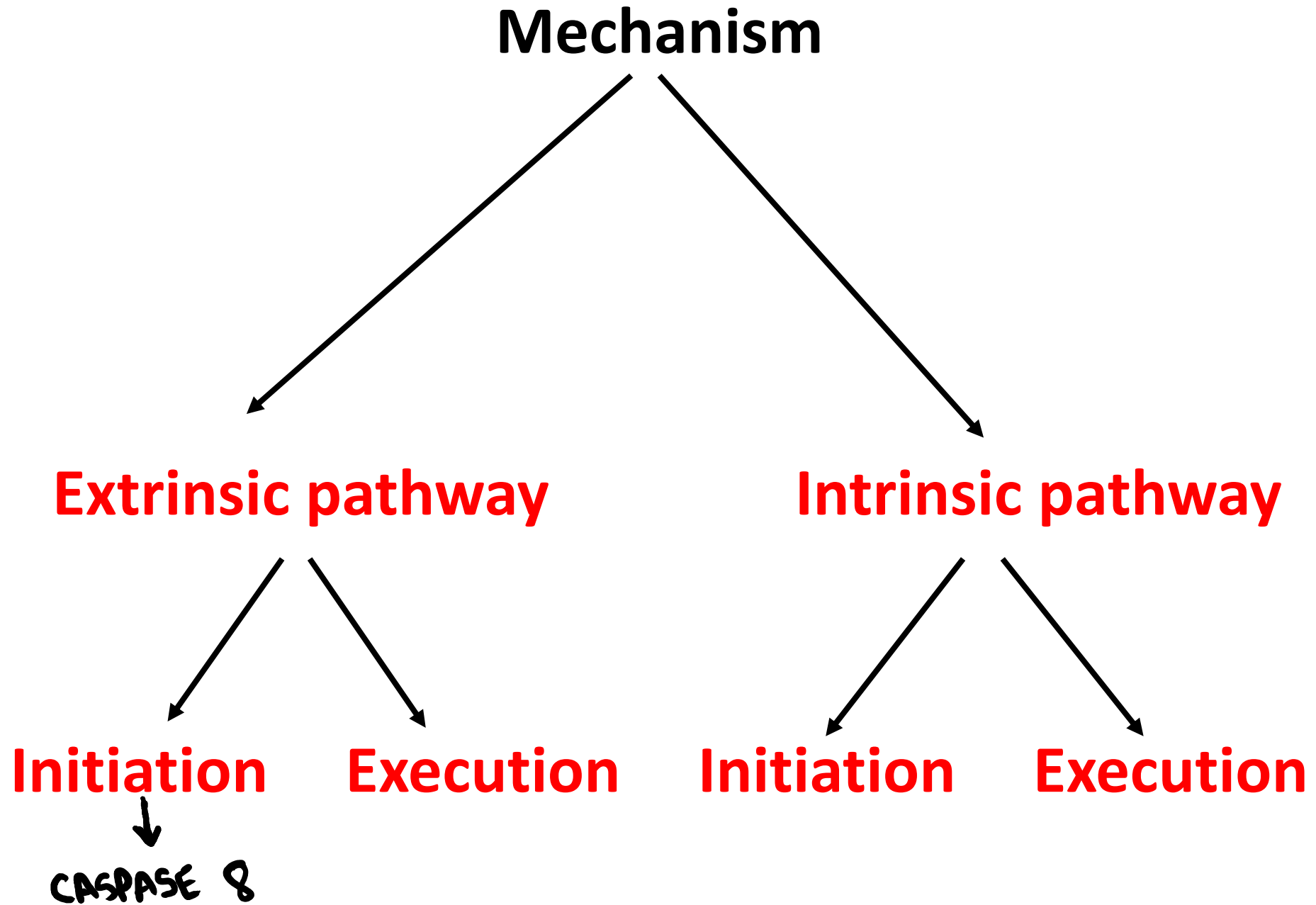
Initiation

Execution

Initiation

Execution

CASPASE 8



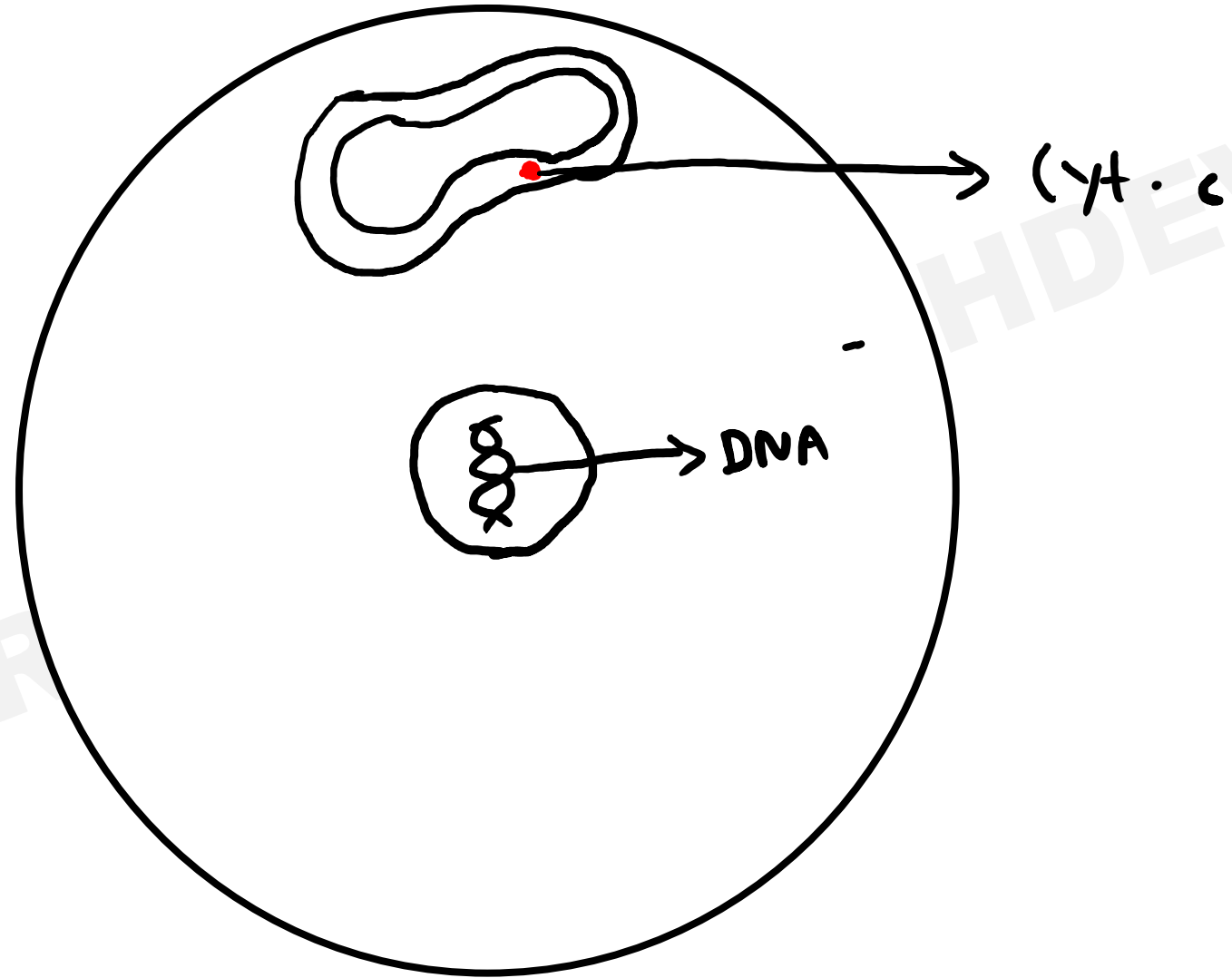
Intrinsic pathway → Initiation phase

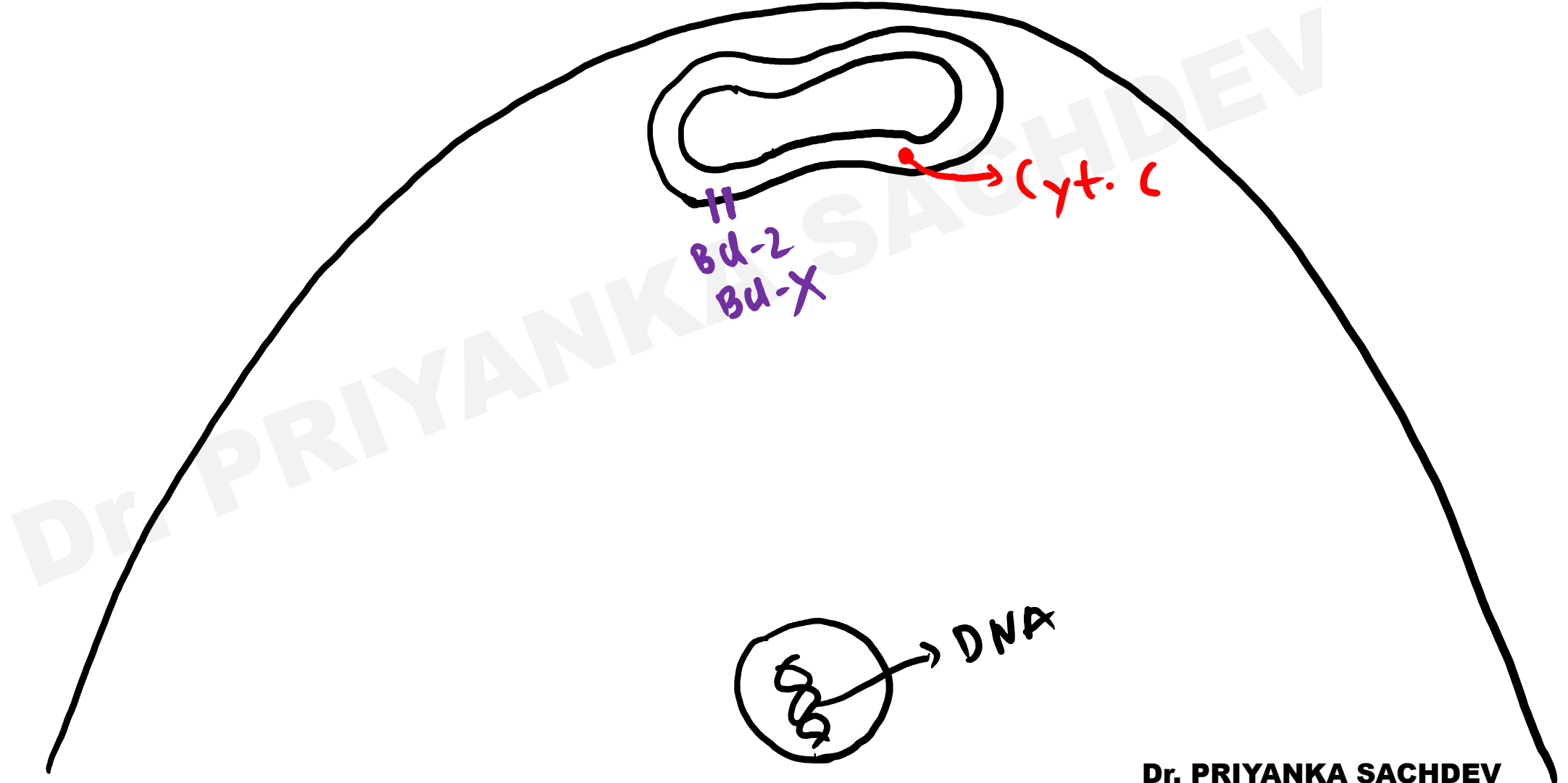
- The intrinsic signaling pathways that initiate apoptosis involve a diverse array of **non-receptor-mediated stimuli** that produce intracellular signals within the cell and are **mitochondrial-initiated events**

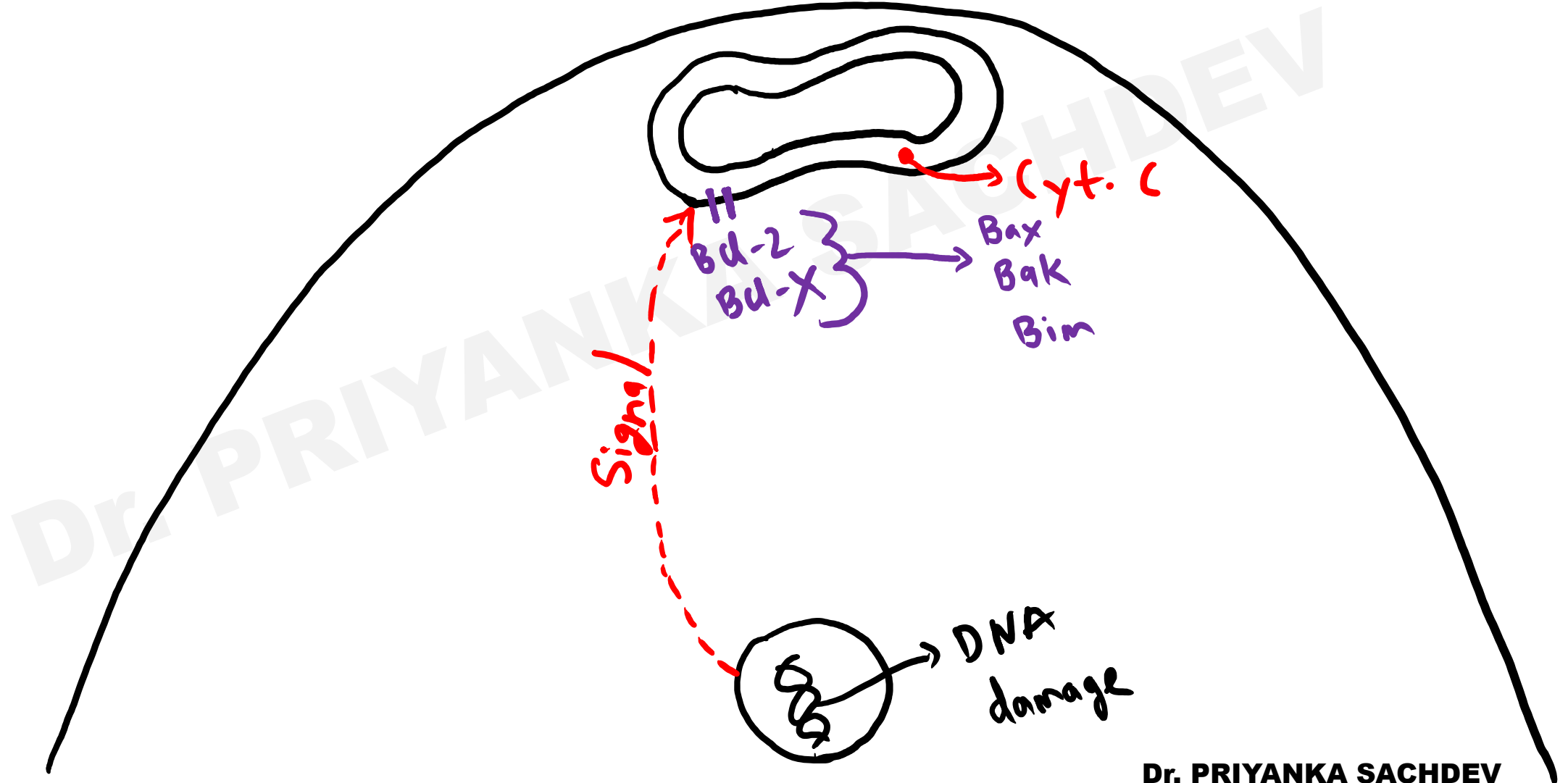
Stimuli

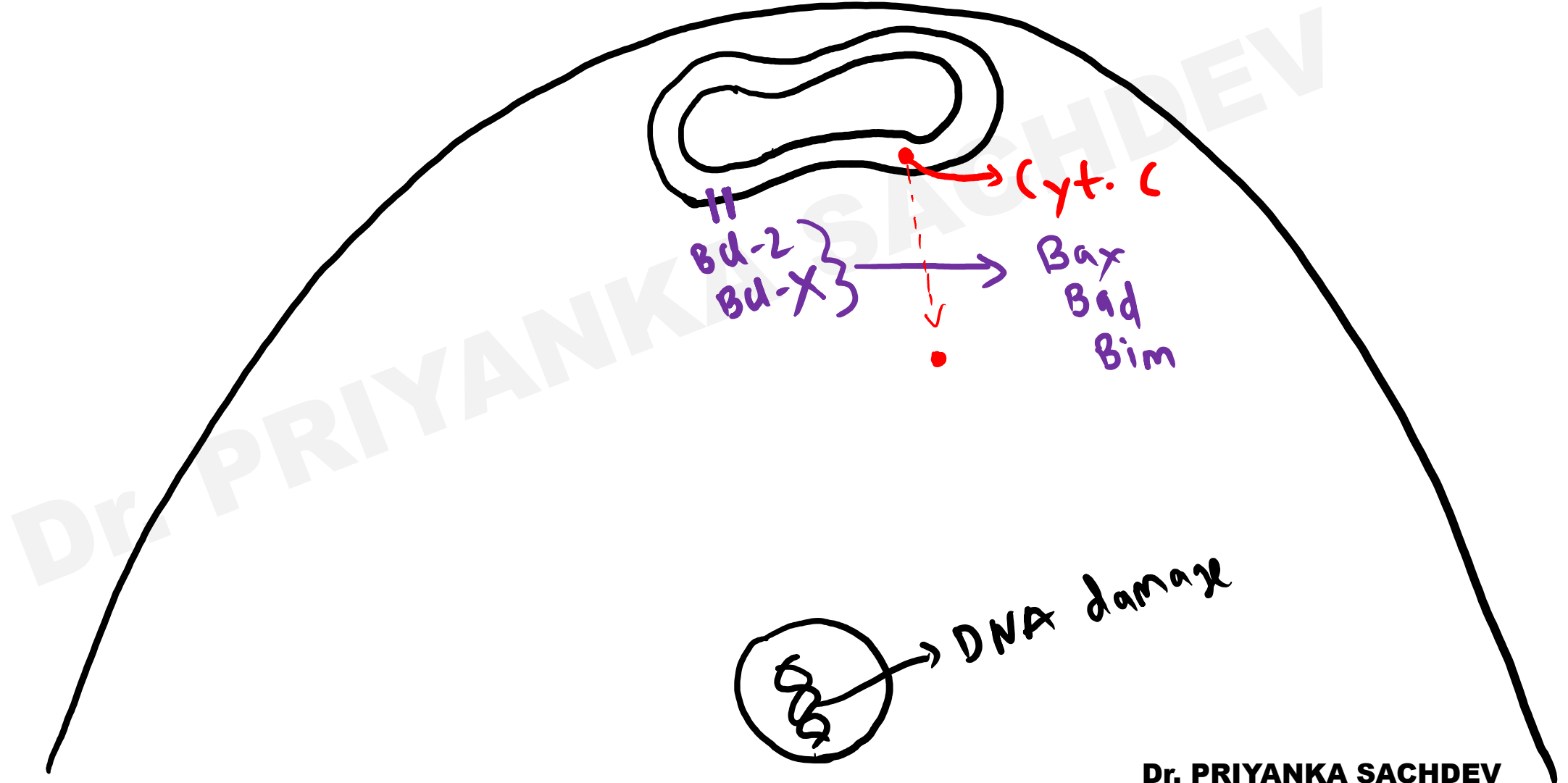
DNA damage (beyond repair)

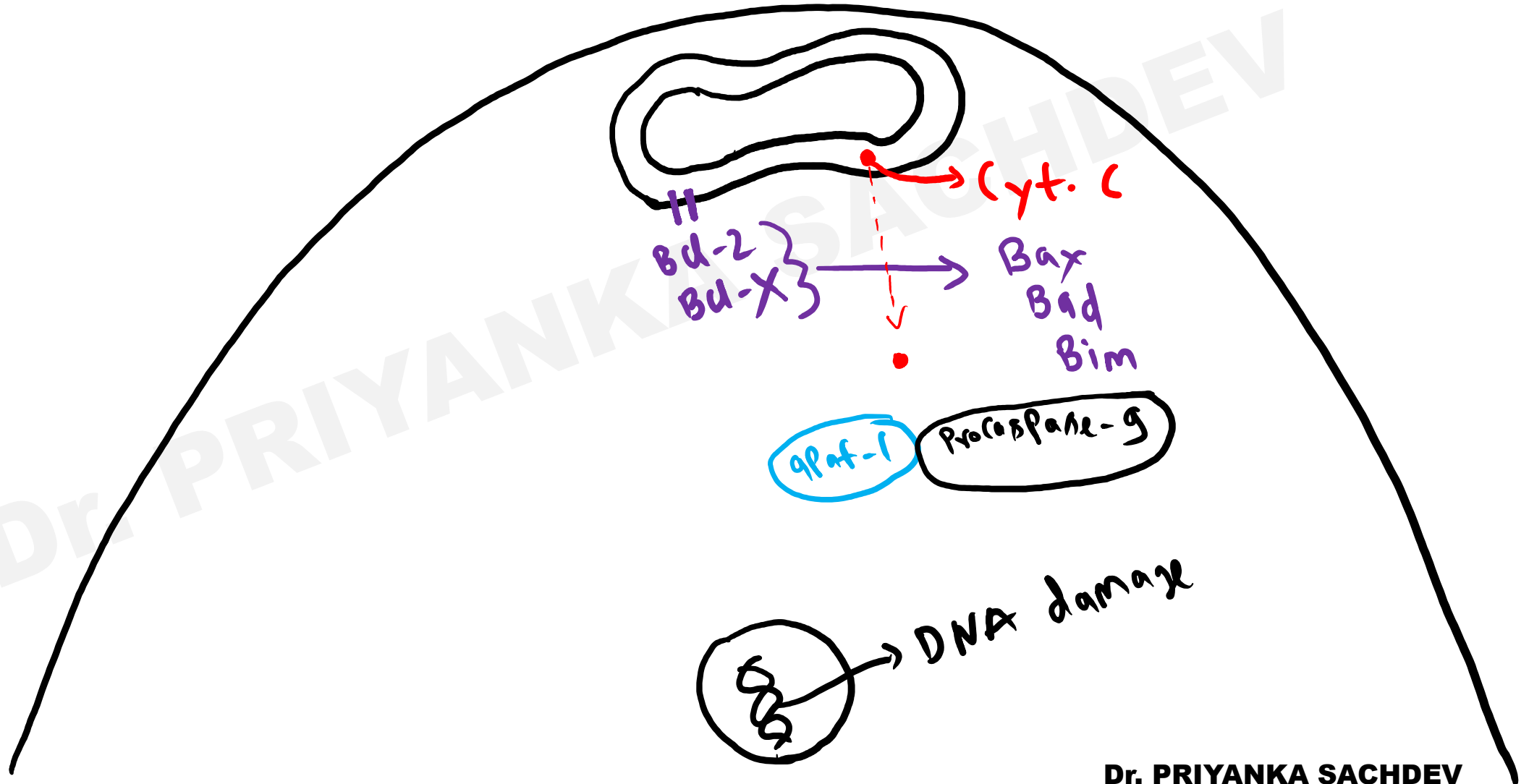
DNA damage can occur after exposure to agents like radiation and chemotherapy (genotoxic stress)

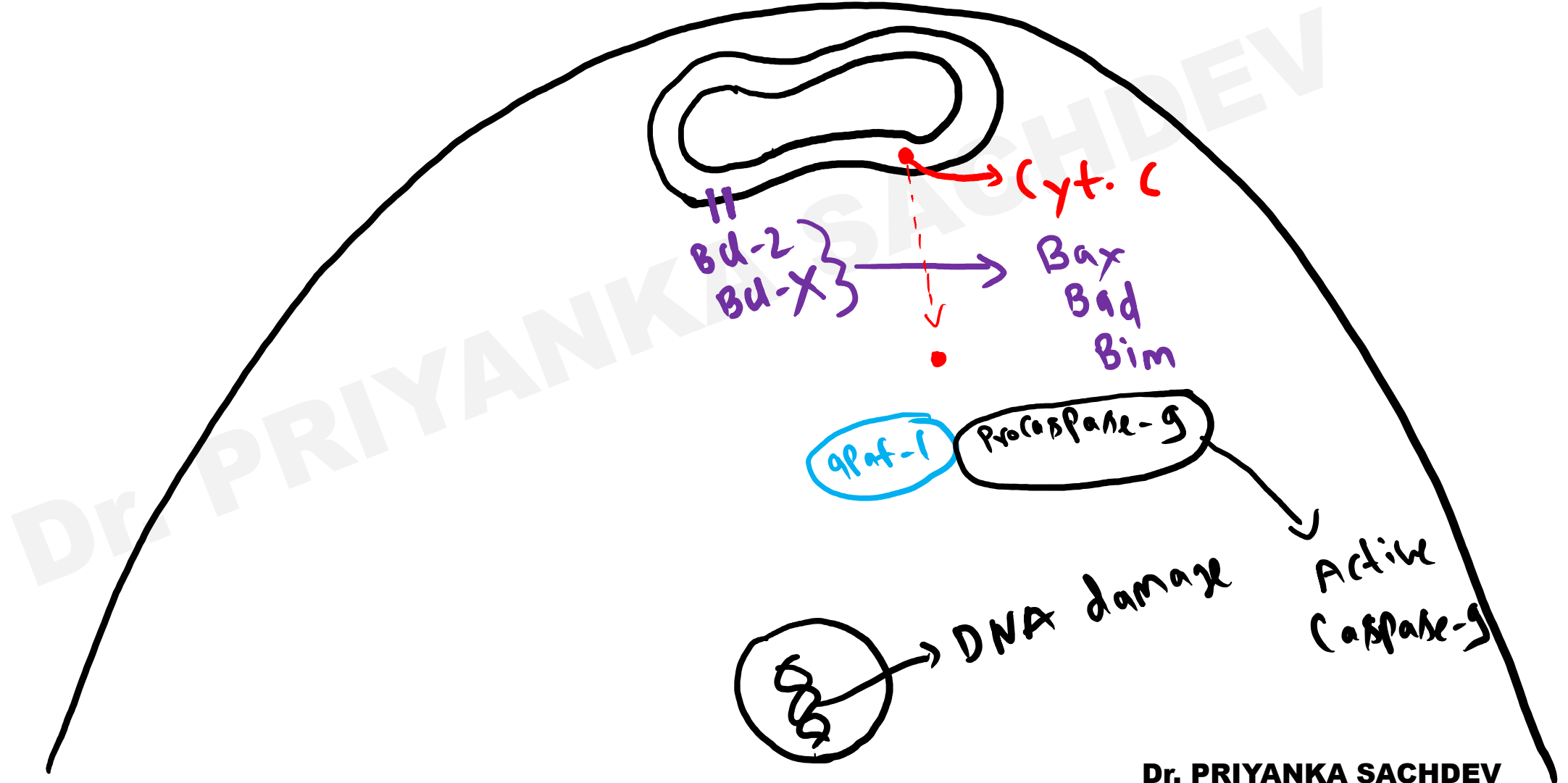


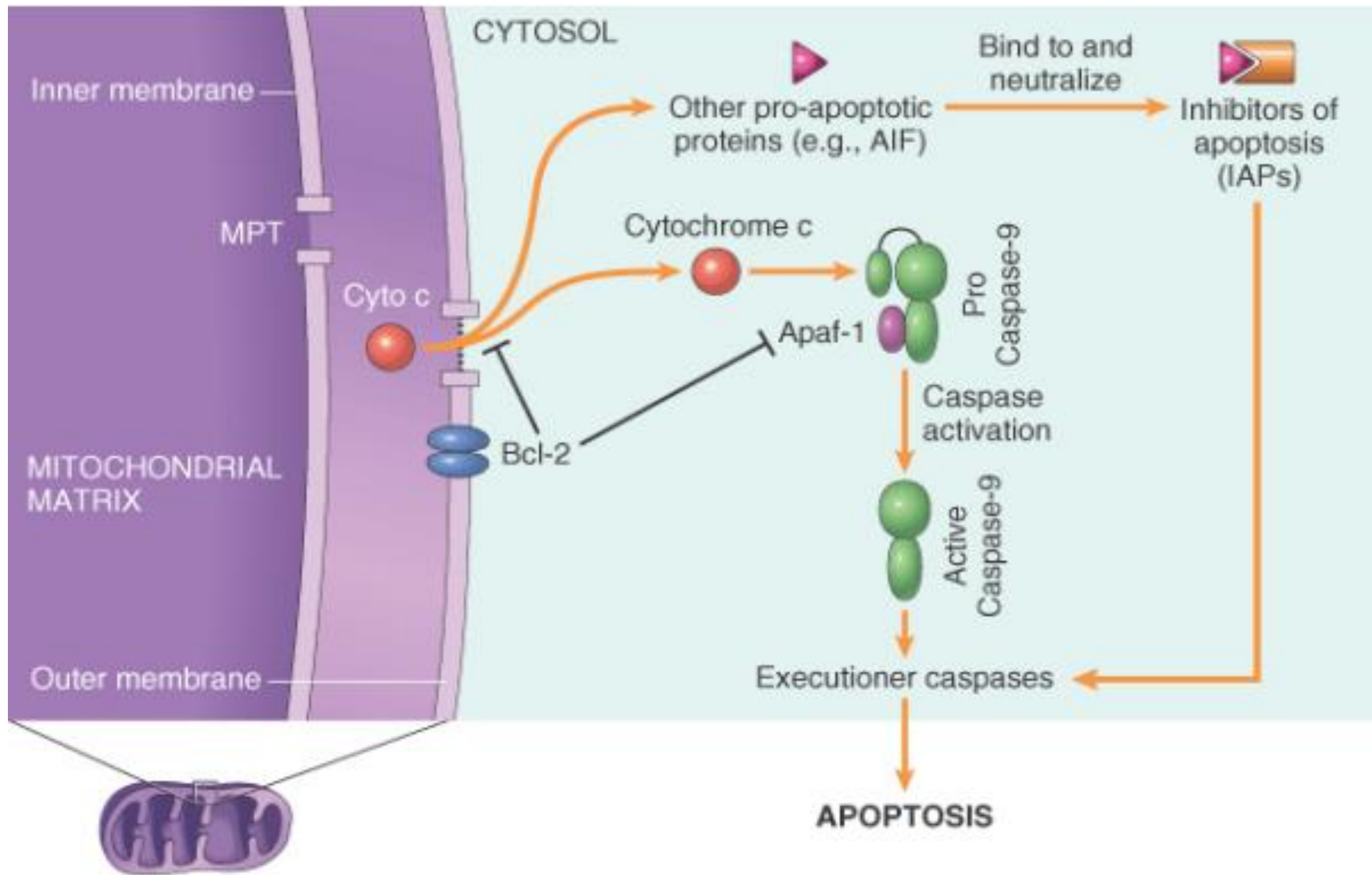












Stimuli



Anti apoptotic molecules **Bcl-2 and **Bcl-x** are lost**



Replaced by pro-apoptotic molecules like **Bak, **Bax**, **Bim****



Increased mitochondrial permeability (MPT)



Release to cytochrome C into cytoplasm



Activates Apaf-1 along with procaspase-9



Activated caspase-9

Antiapoptotic molecules

1. BCL-2
2. BCL-X
3. Mcl-1
4. FLIP

Proapoptotic molecules

1. Bax
2. Bim
3. Bad
4. Bak
5. P53 gene
6. Apaf-1
7. Cytochrome C

REMEMBER

- **Mitochondria** are the most important organelles involved in initiation and regulation of apoptosis
- **Mitochondrial membrane permeabilization** is the hallmark of apoptosis

Mechanism

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Extrinsic pathway

Intrinsic pathway

Initiation

Execution

Initiation

Execution

Mechanism

Extrinsic pathway

Intrinsic pathway

Initiation

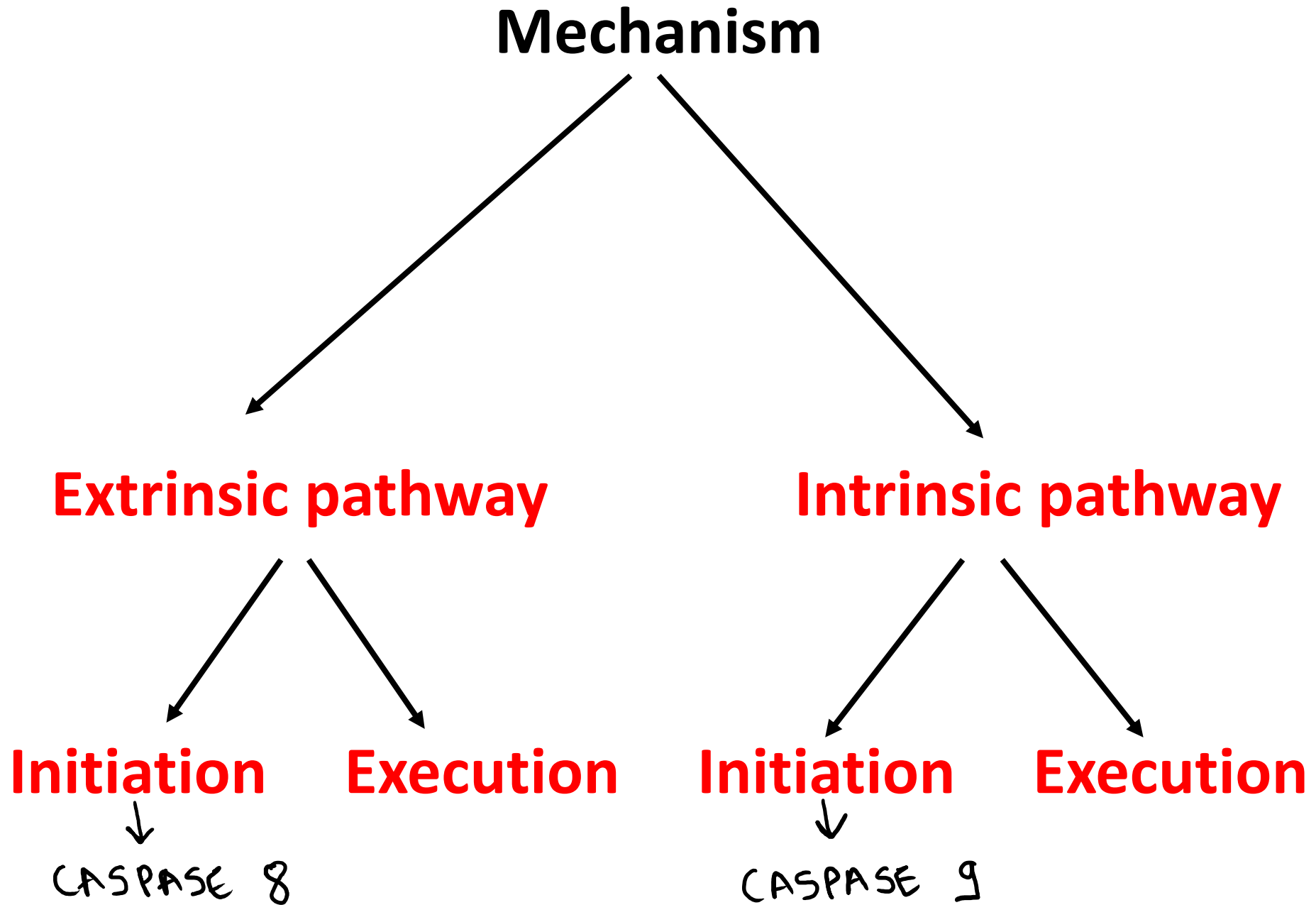
Execution

Initiation

Execution

CASPASE 8

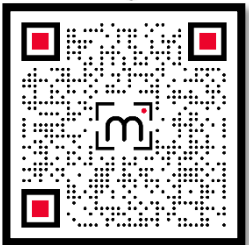
CASPASE 9



Execution phase

- It is a **convergence point** for both extrinsic and intrinsic pathways.

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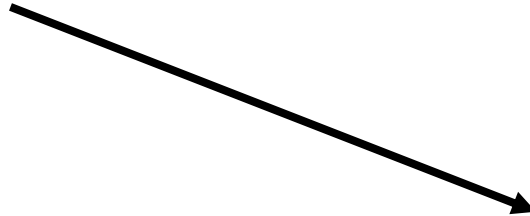


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Extrinsic pathway



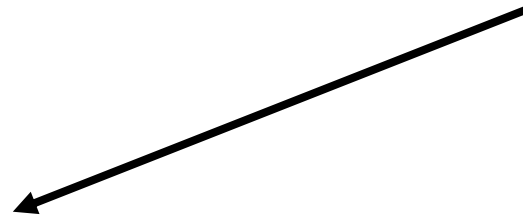
Caspase 8



Intrinsic pathway



Caspase 9



Activates caspase 3 and 7



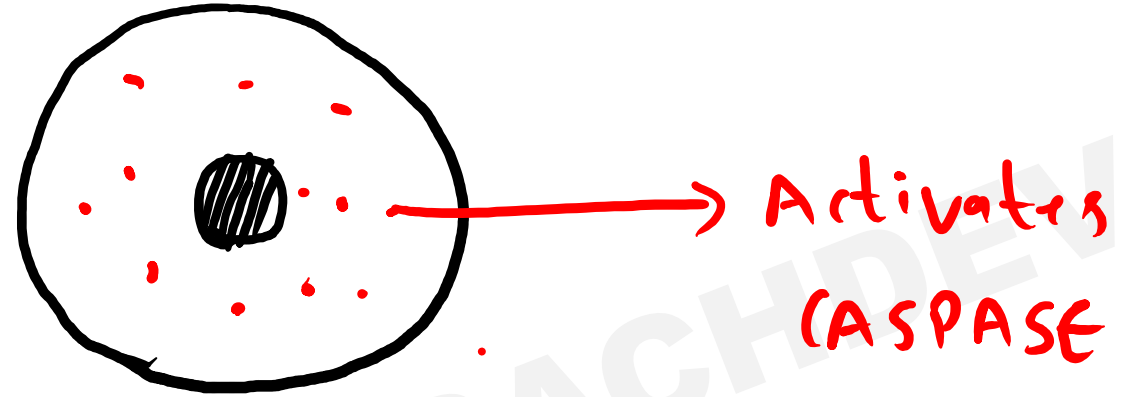
Sequentially activates all other caspase



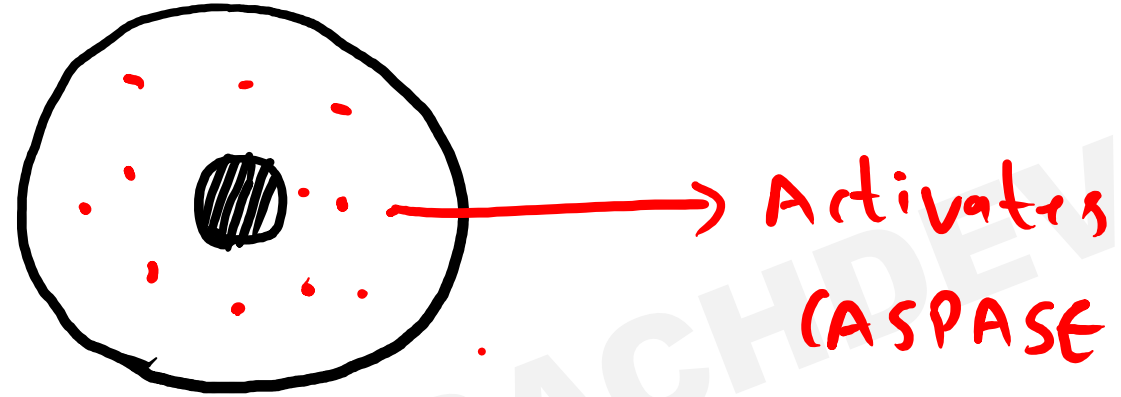
Caspases cleave cytoskeletal and nuclear matrix proteins

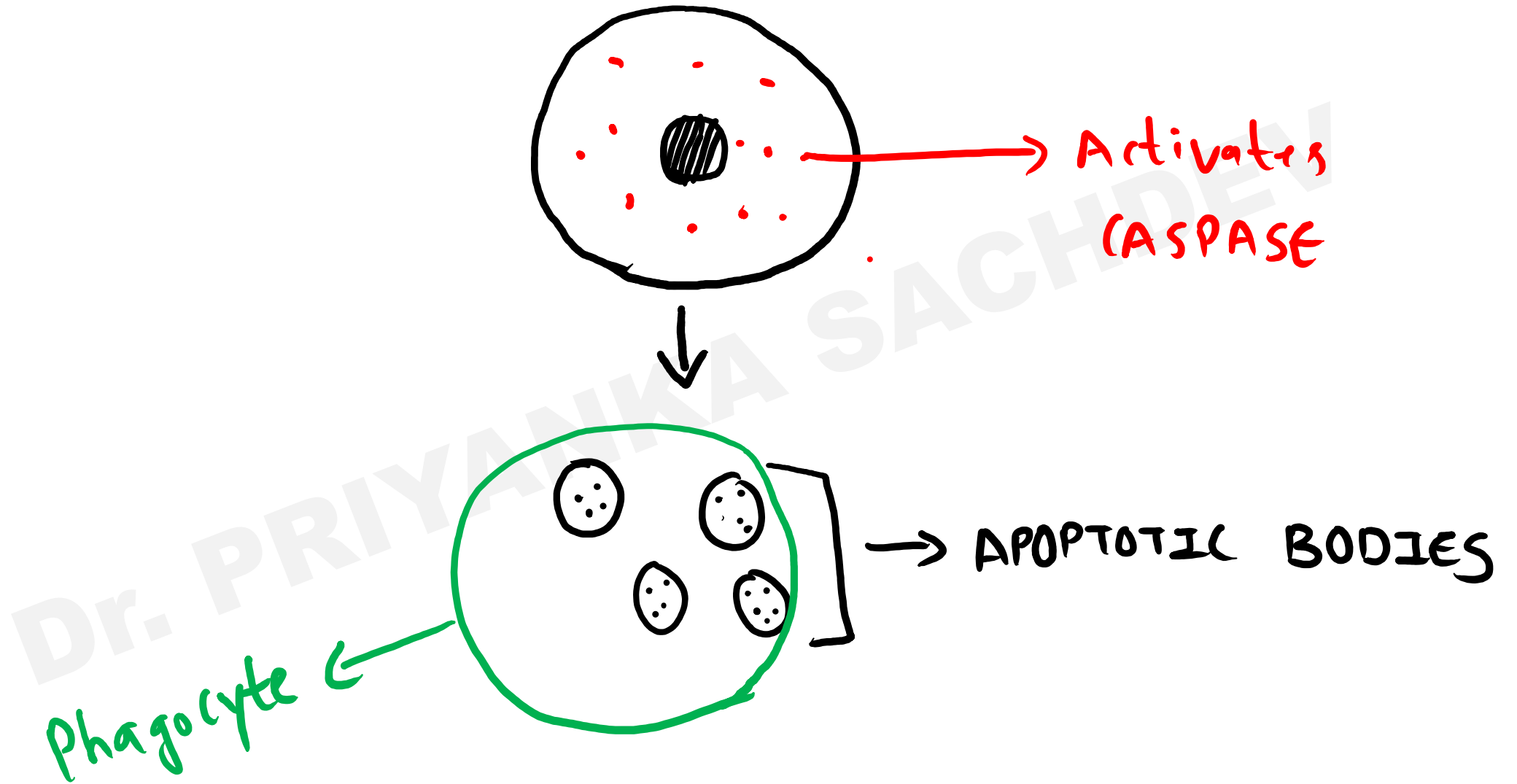


Cell degenerate/ apoptotic bodies formed



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REMEMBER

- Initiation Caspase → **CASPASE 8 and 9**
- Execution Caspase → **CASPASE 3 and 7**

Mechanism

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Extrinsic pathway

Intrinsic pathway

Initiation

Execution

Initiation

Execution

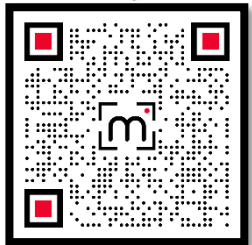
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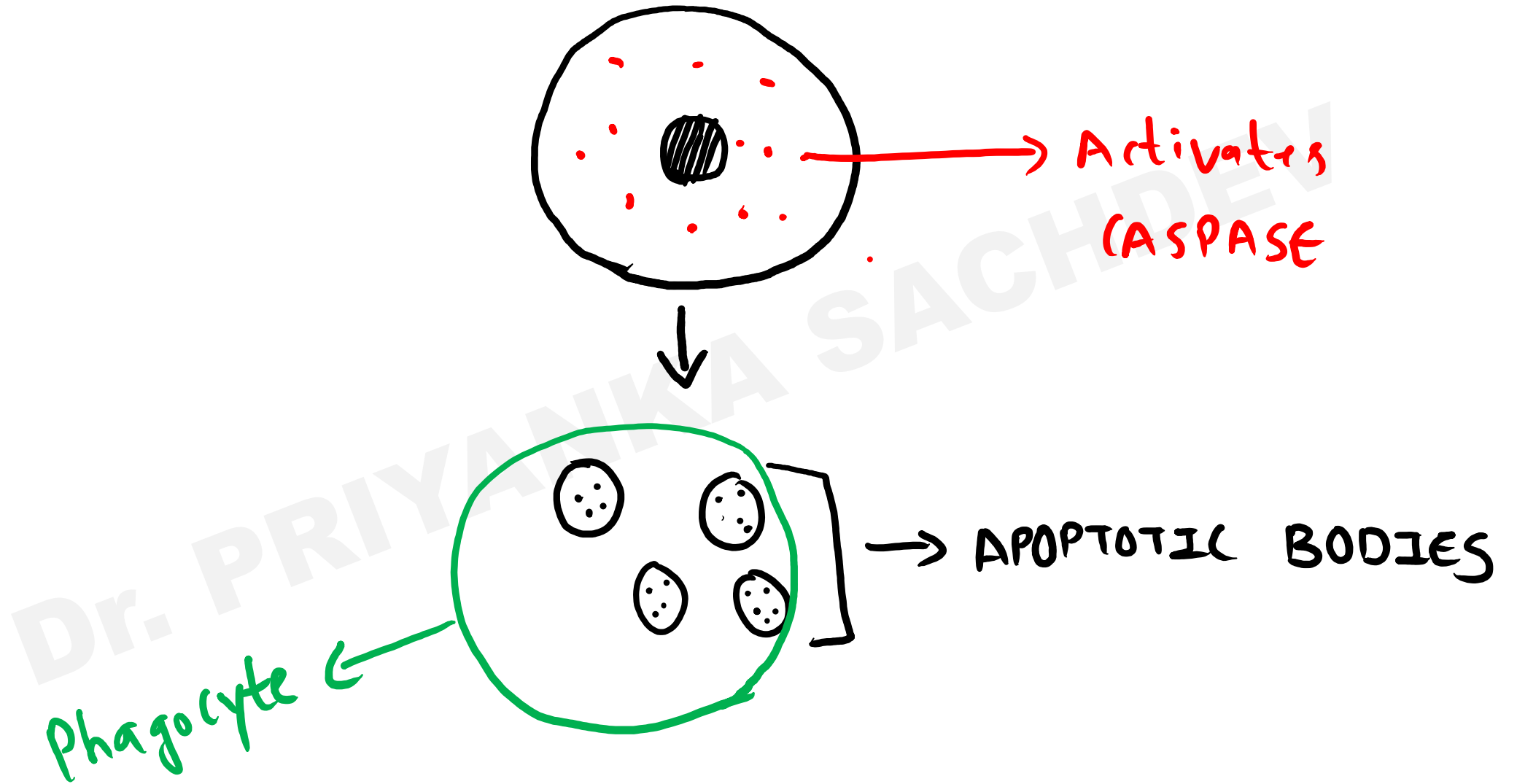
Phagocytosis

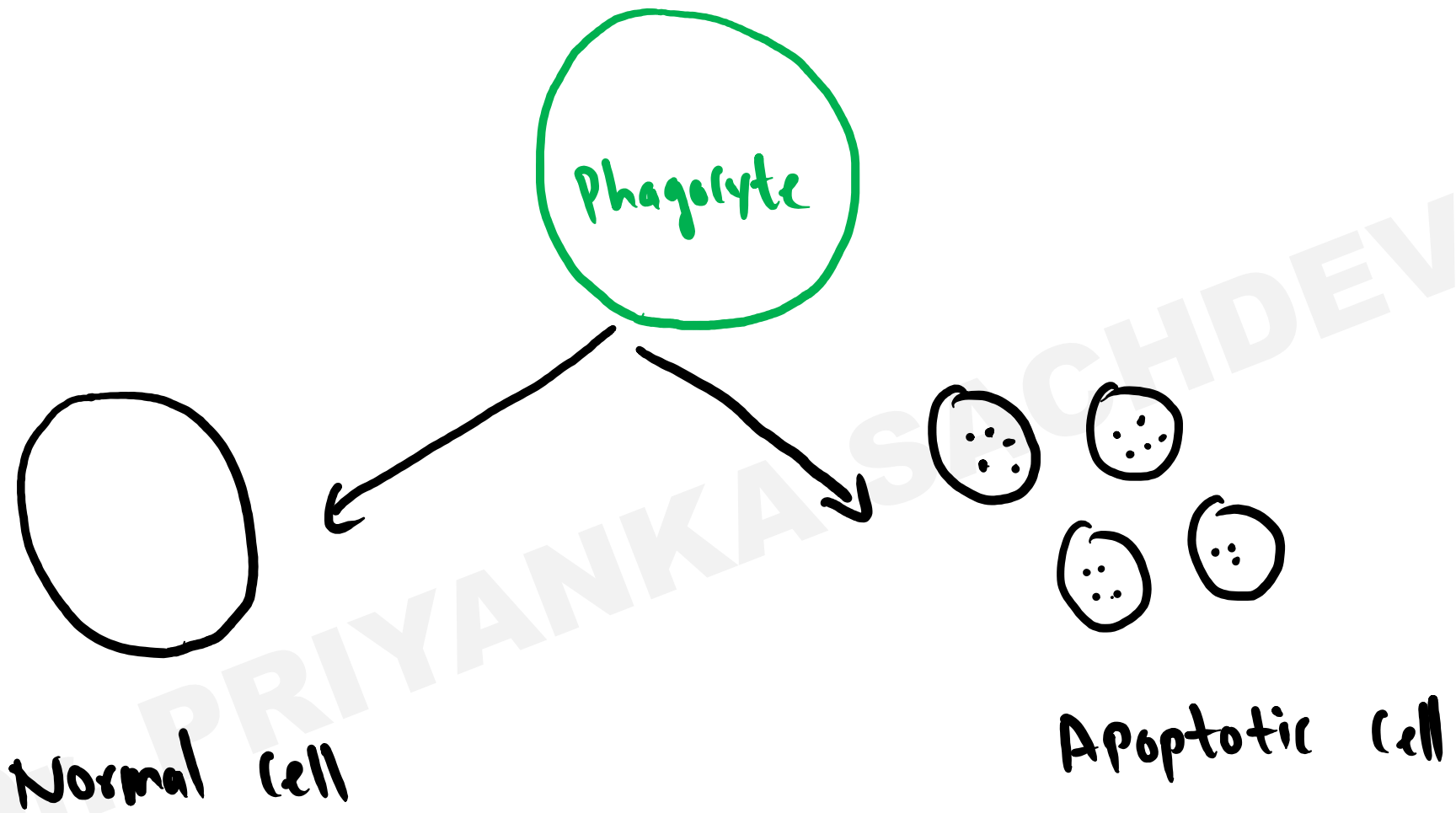


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Phosphatidylserine is a phospholipid present on inner surface membrane normally



During apoptosis



Flipped to outer surface

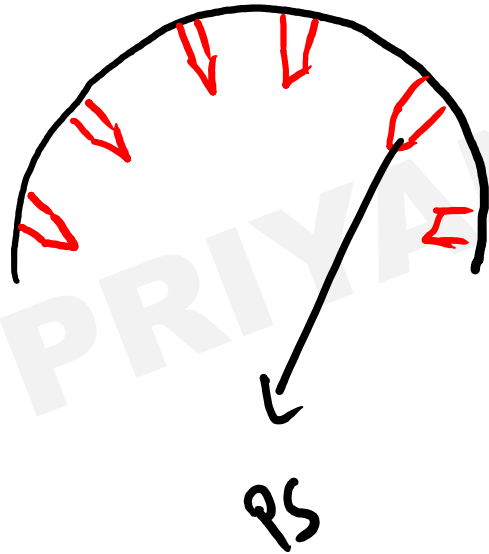


Externalization of phosphatidylserine causes its tagging

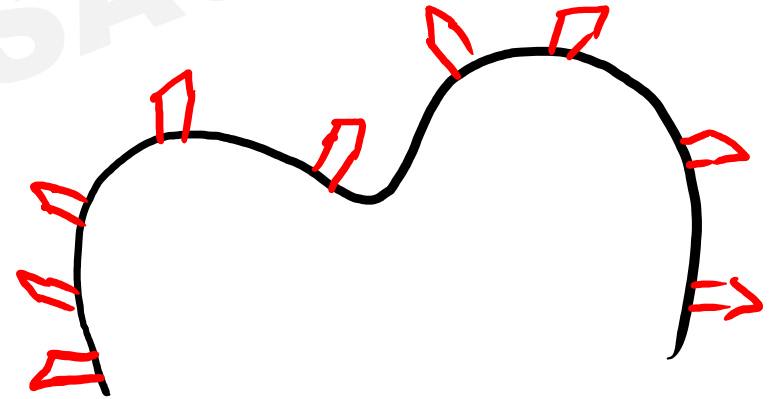


Phagocytes engulf it

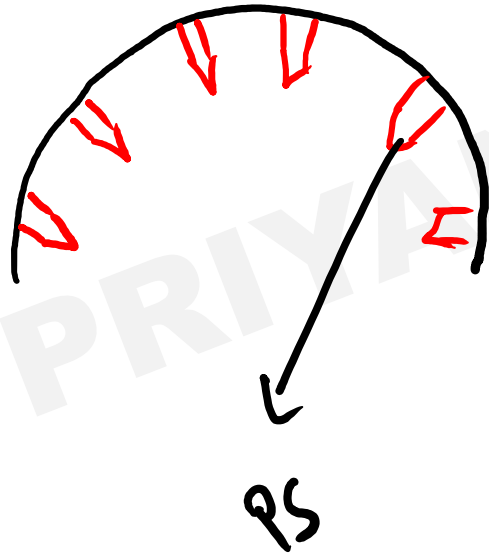
Normally



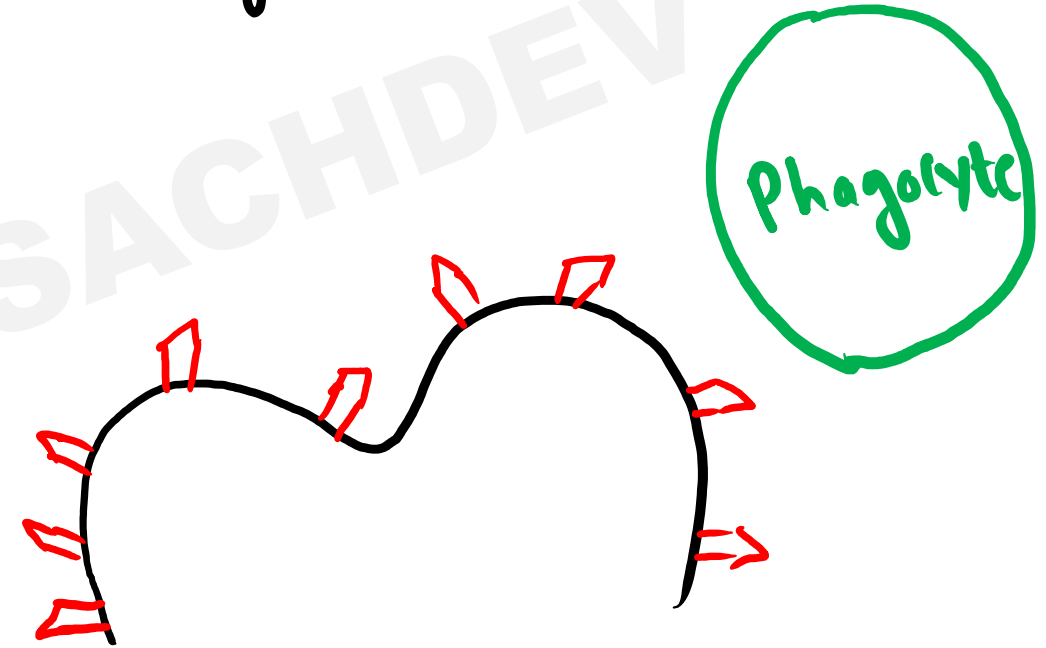
During apoptosis



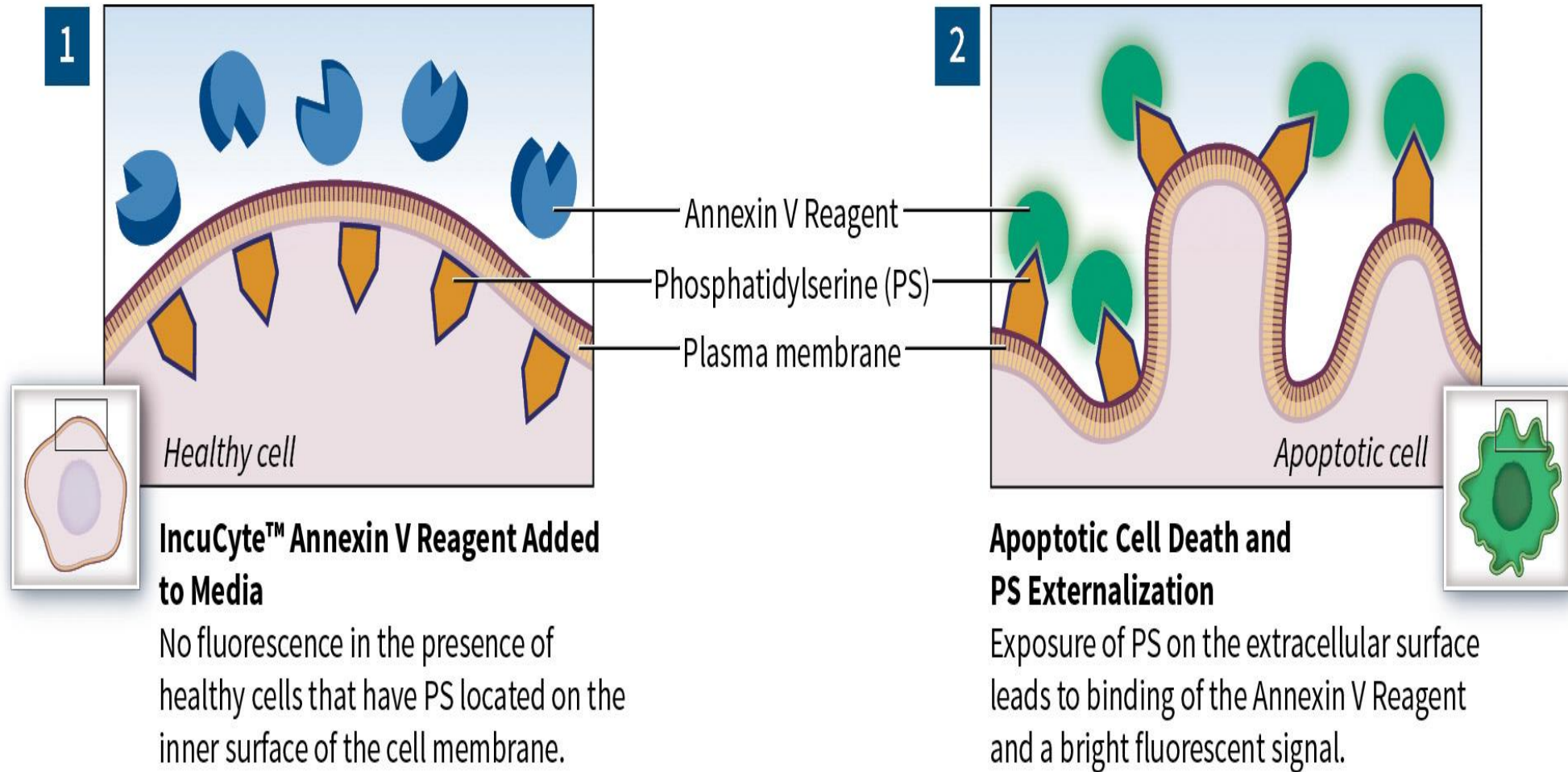
Normally



During apoptosis



Annexin V overview schematic



These alterations permit the early recognition of apoptotic cells by macrophages



Phagocytosis without the release of proinflammatory cellular components.

- The process of apoptotic cells is so efficient that dead cells disappear without leaving a trace and **inflammation is virtually absent.**

- Essential feature is immediate, specific and non-inflammatory nature of phagocytosis

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POLLS 2

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CD 95 is a marker of -

- a) Intrinsic pathway of apoptosis**
- b) Extrinsic pathway of apoptosis**
- c) Monocyte**
- d) Leucocyte**

CD 95 is a marker of -

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In apoptosis, cytochrome C acts through

- a) Apaf 1**
- b) Bcl-2**
- c) FADD**
- d) TNF**

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The following is an antiapoptotic gene -

- a) Bax
- b) Bad
- c) Bcl-X
- d) Bim

The following is an antiapoptotic gene -

- a) Bax
- b) Bad
- **c) Bcl-X**
- d) Bim

Which of the following organelles plays a pivotal role in apoptosis?

- a) Mitochondria
- b) Endoplasmic reticulum
- c) Nucleus
- d) Golgi apparatus

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Antiapoptotic protein among the following is?

- a) MCL-1
- b) P53
- c) BAX
- d) BIM

Dr. PK

A

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OVERVIEW

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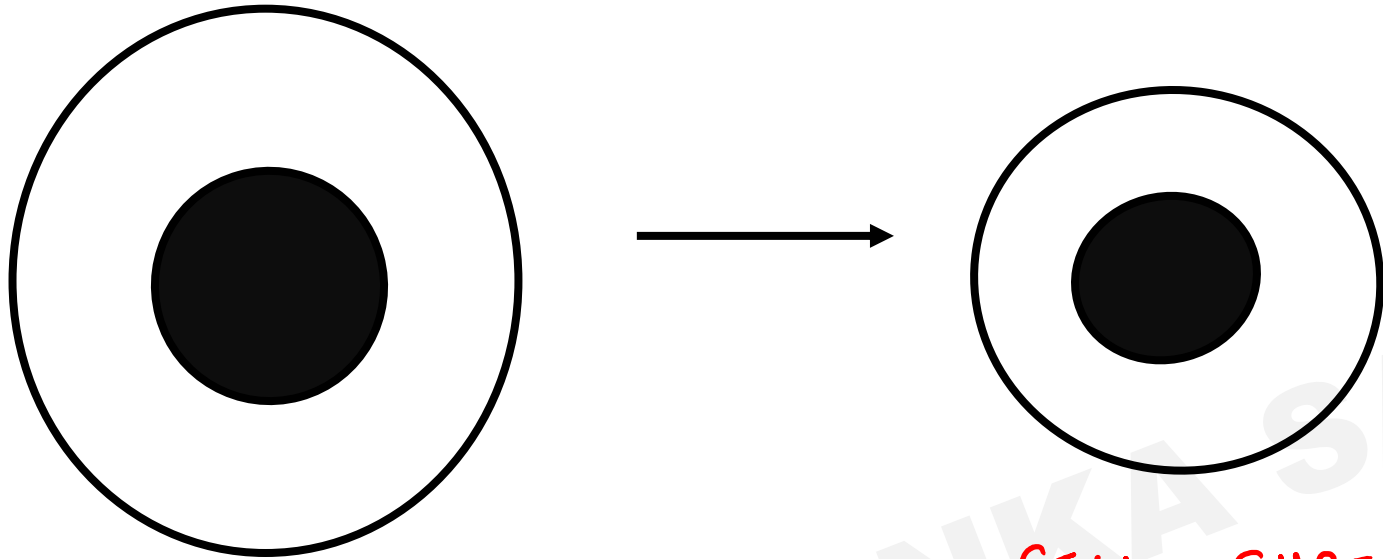
Morphological changes in apoptosis

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1. Cellular shrinkage is **earliest change**

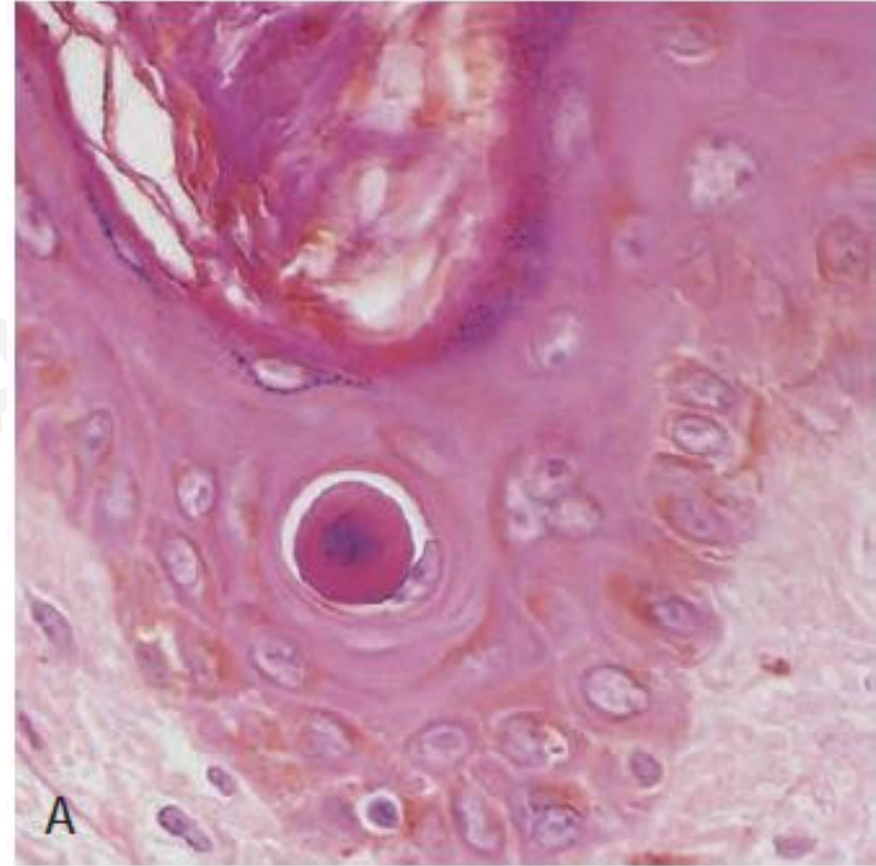
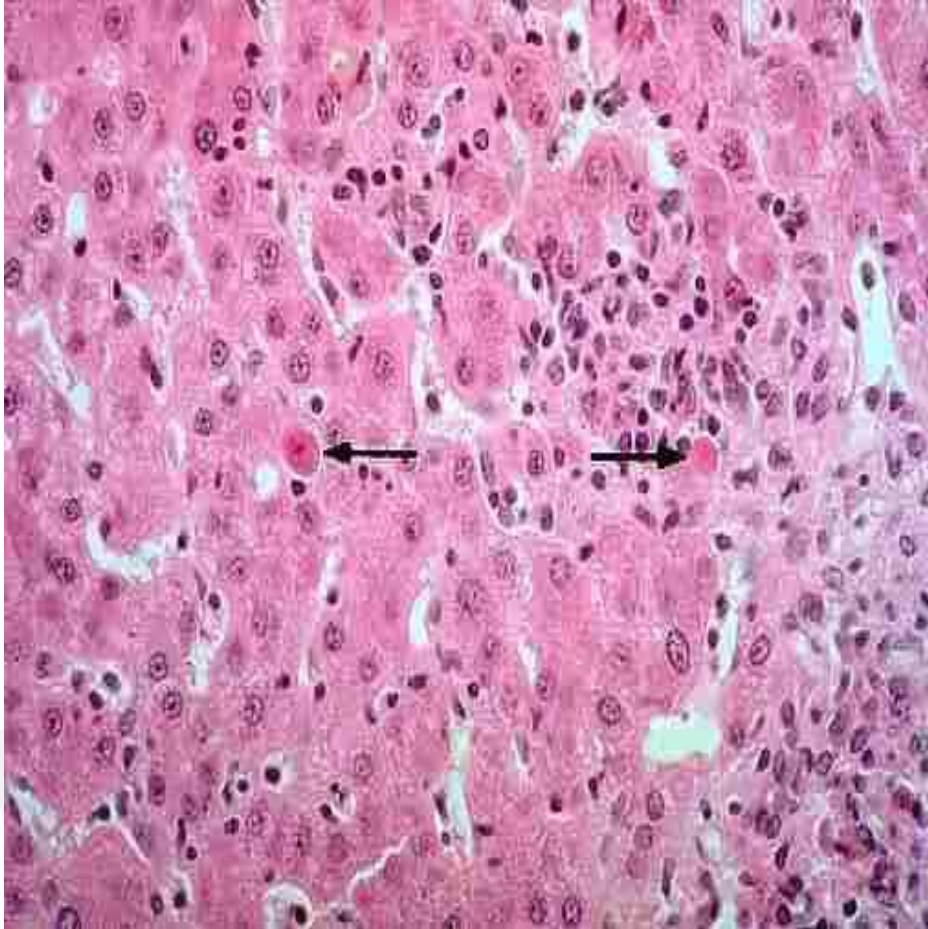
- It is due to damage to cytoskeletal proteins.

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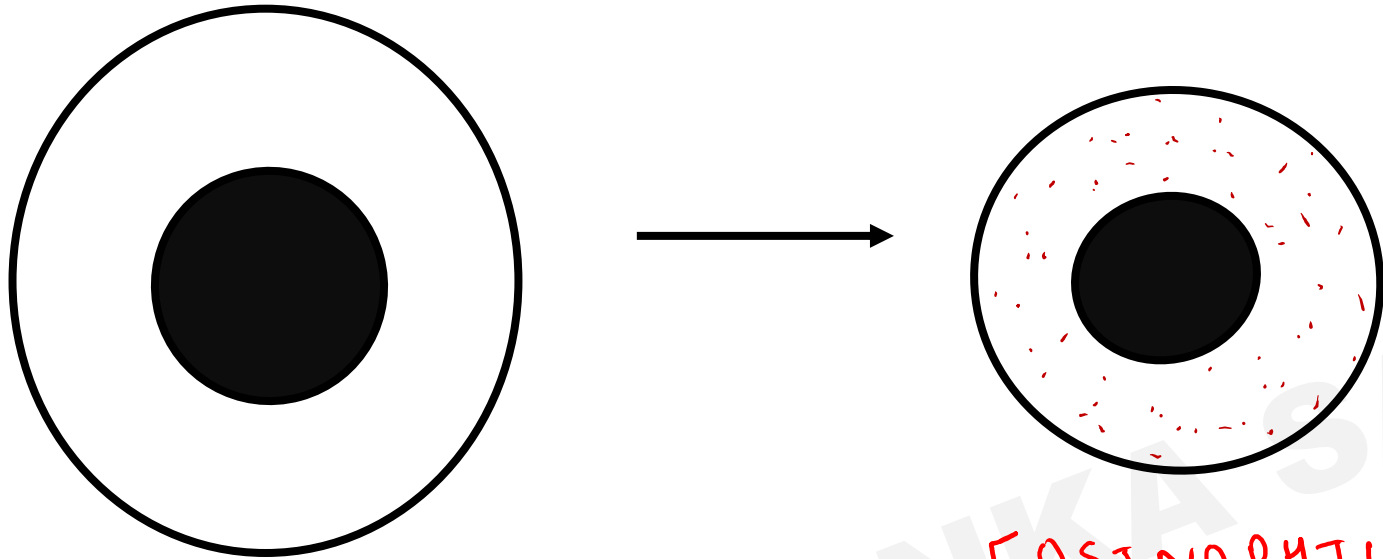
CELL SHRINKAGE

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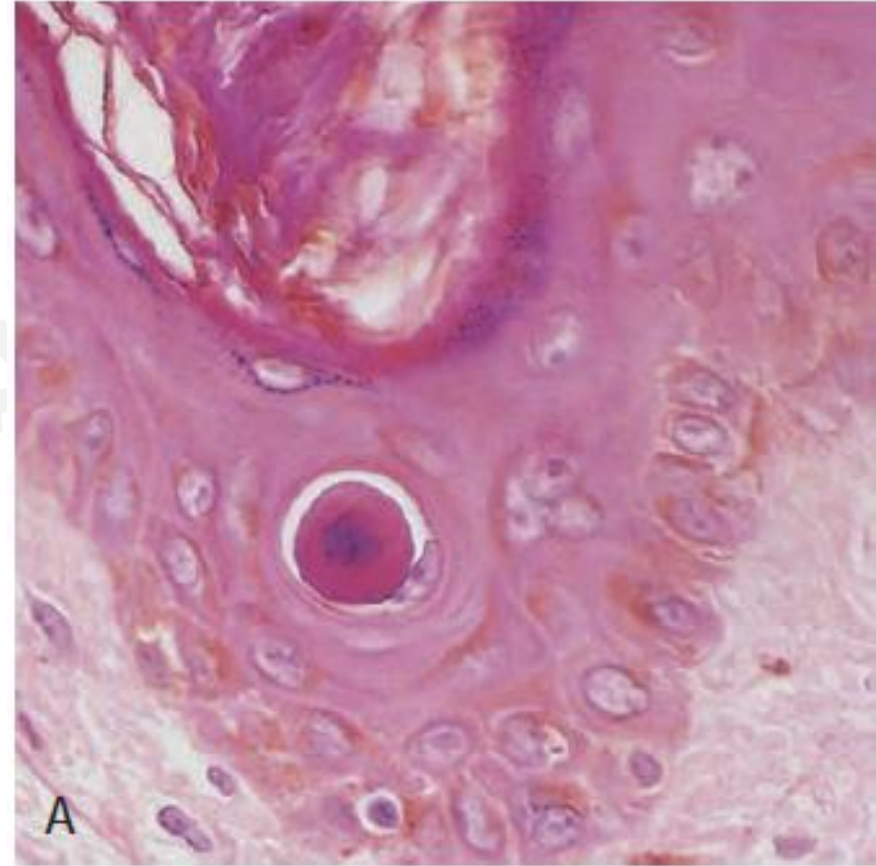
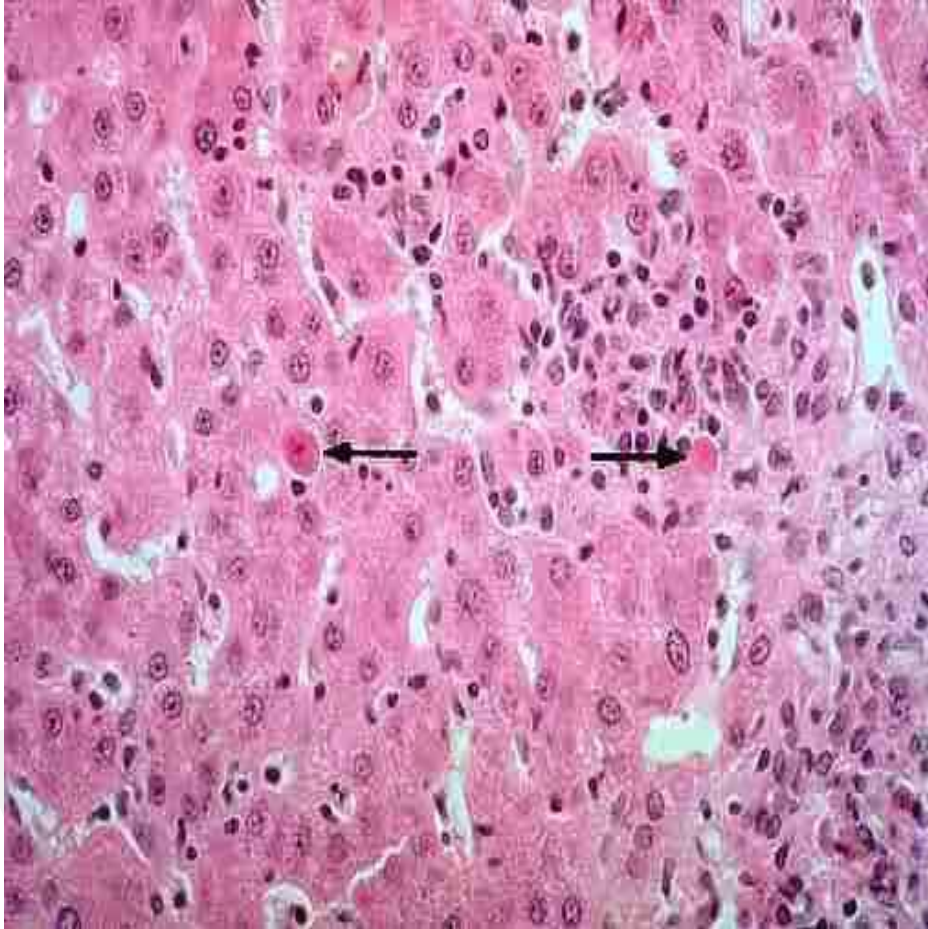
2. Cellular organelles are tightly packed thus imparting intense **eosinophilic** color to cytoplasm

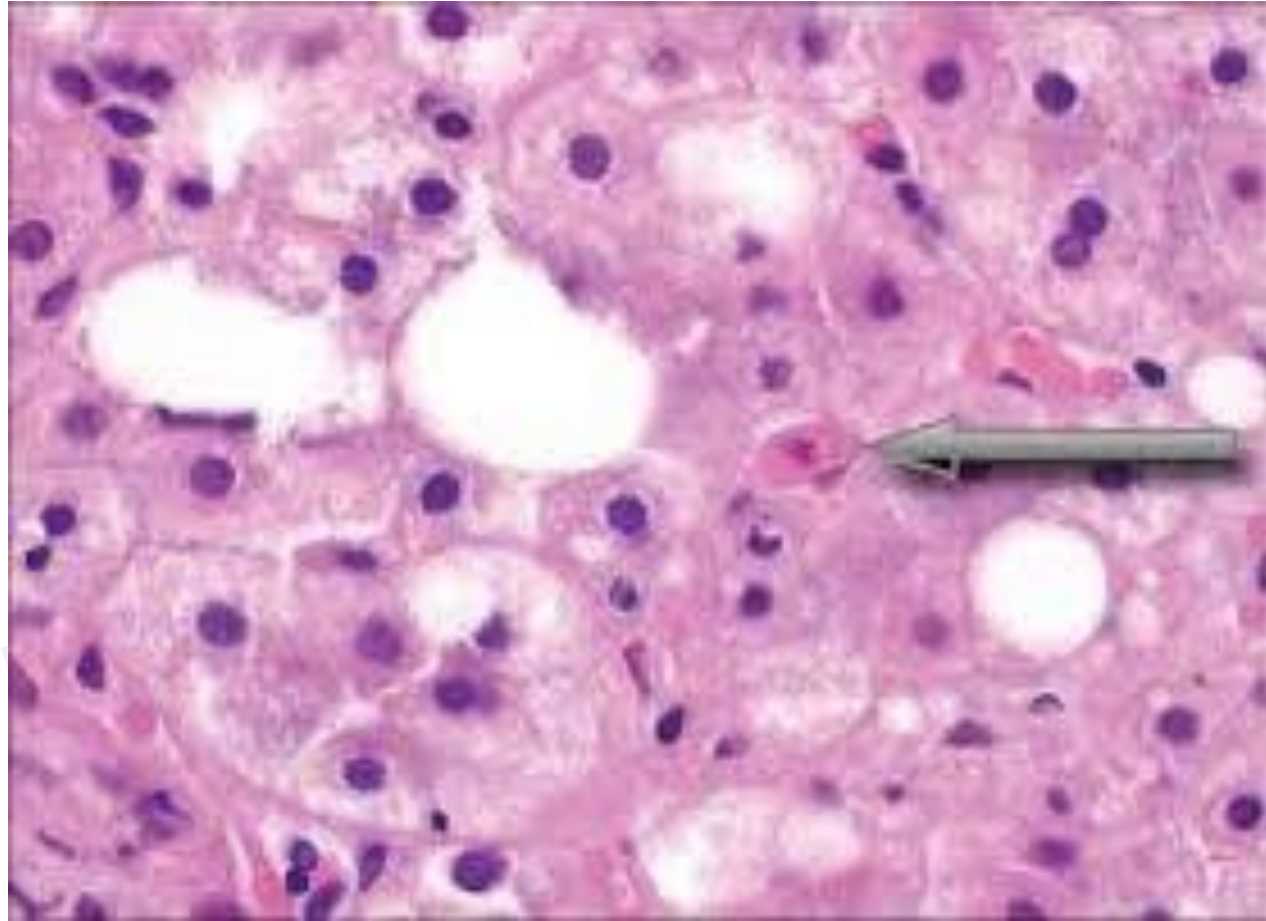
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EOSINOPHILIA

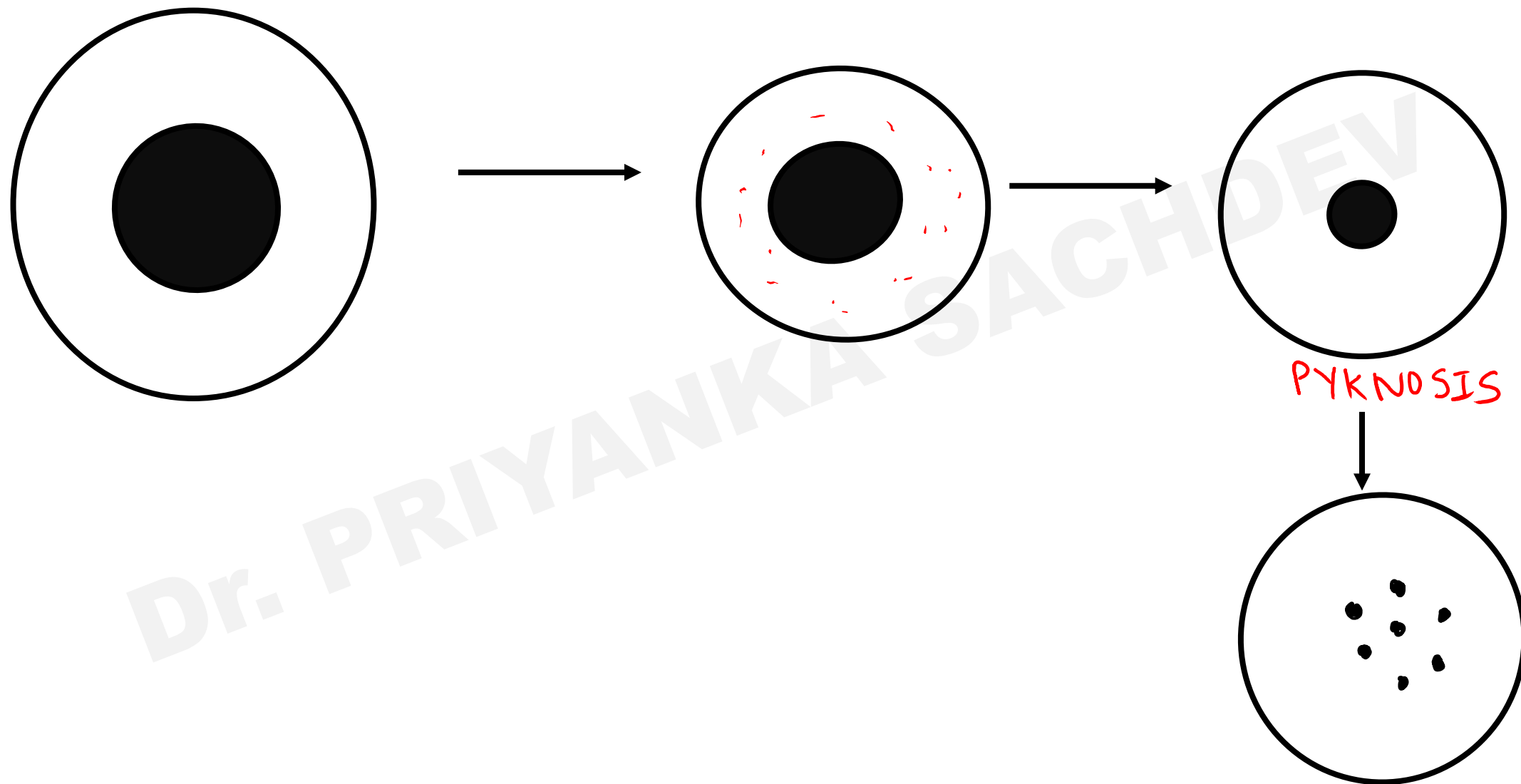
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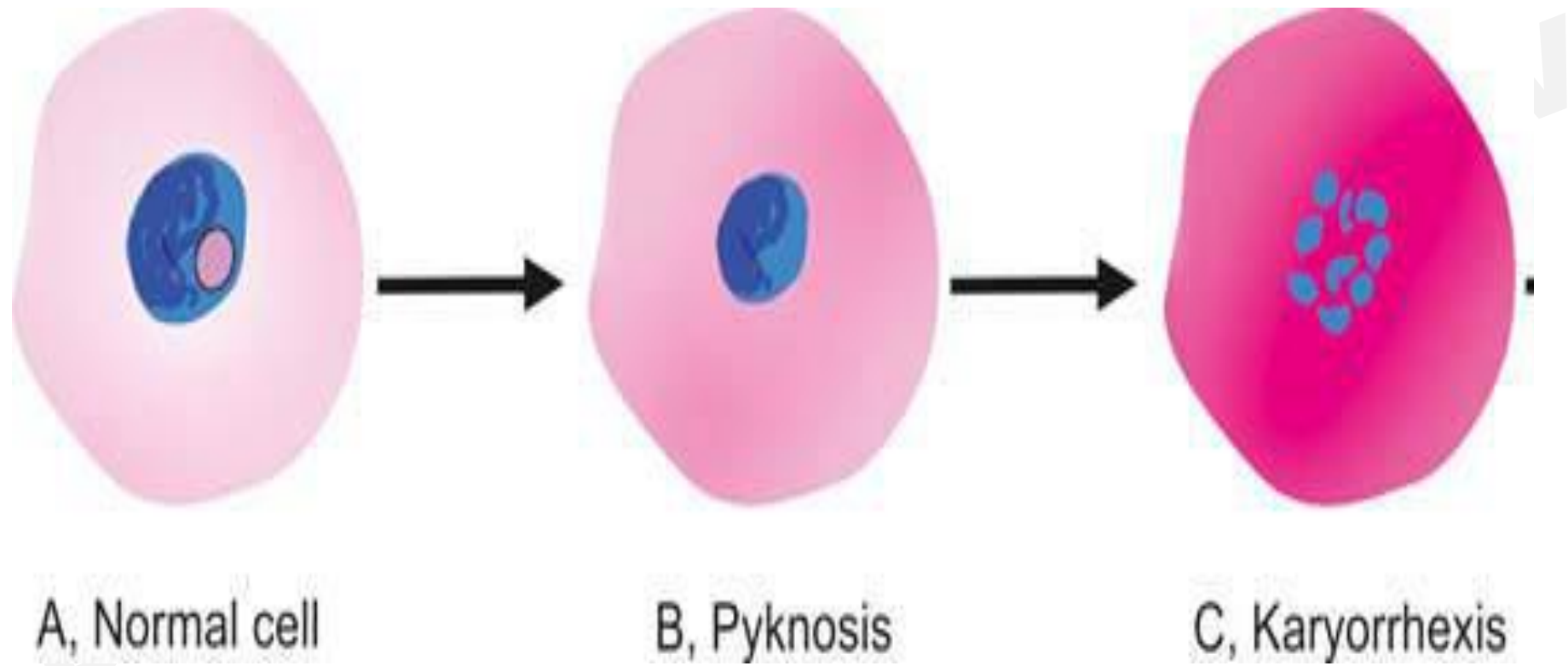
3. Nuclear changes

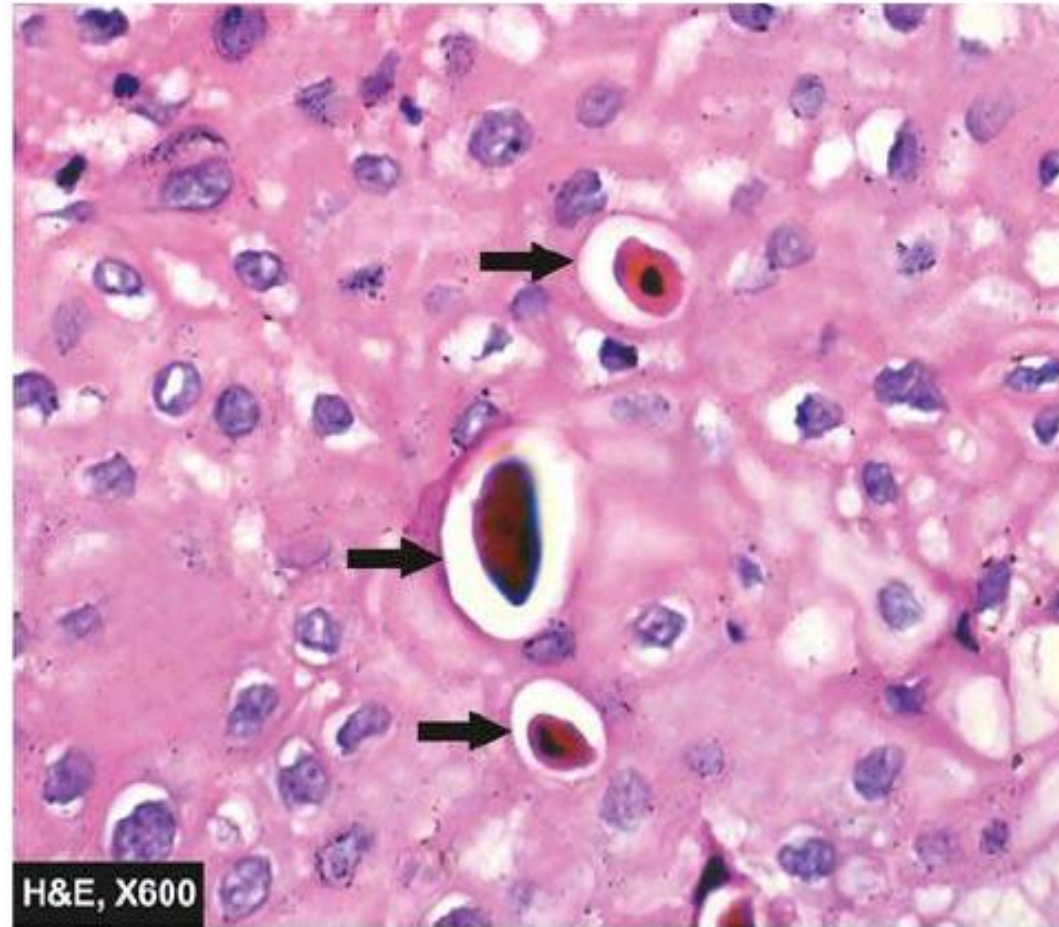
- **Pyknosis** ie. Chromatin condensation or nuclear compaction
- **Karyorrhexis** ie. nuclear fragmentation. It is due to activity of endonuclease and caspases
- It is the **most characteristic feature**

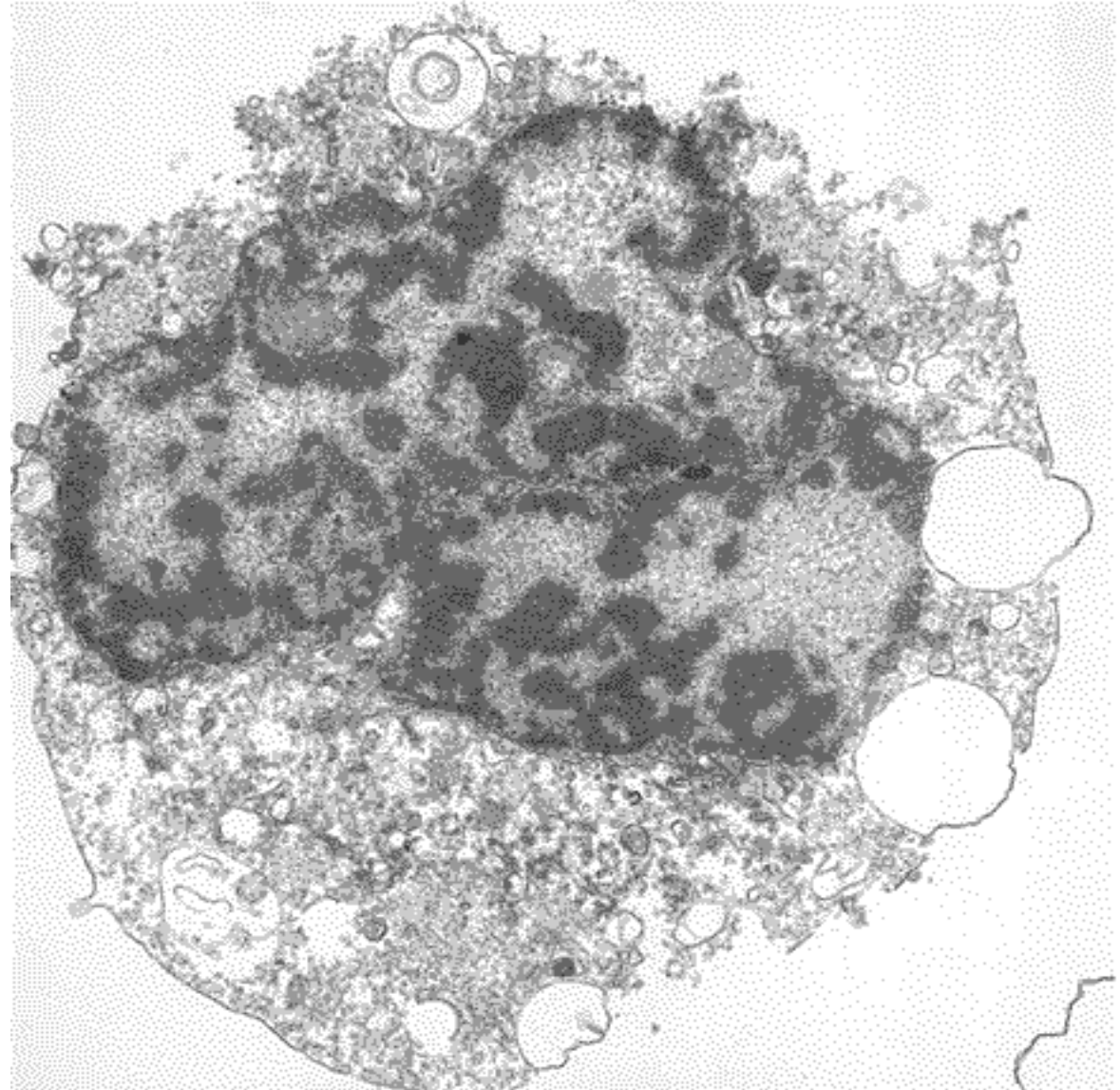
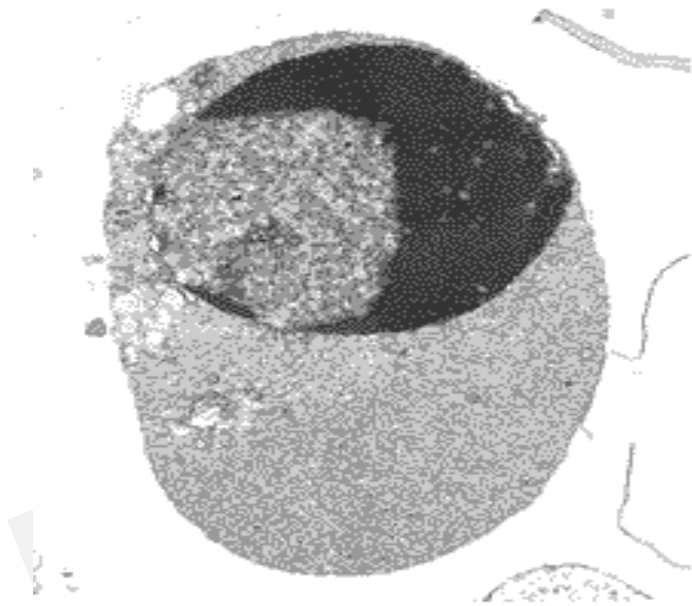


PYKNOSIS

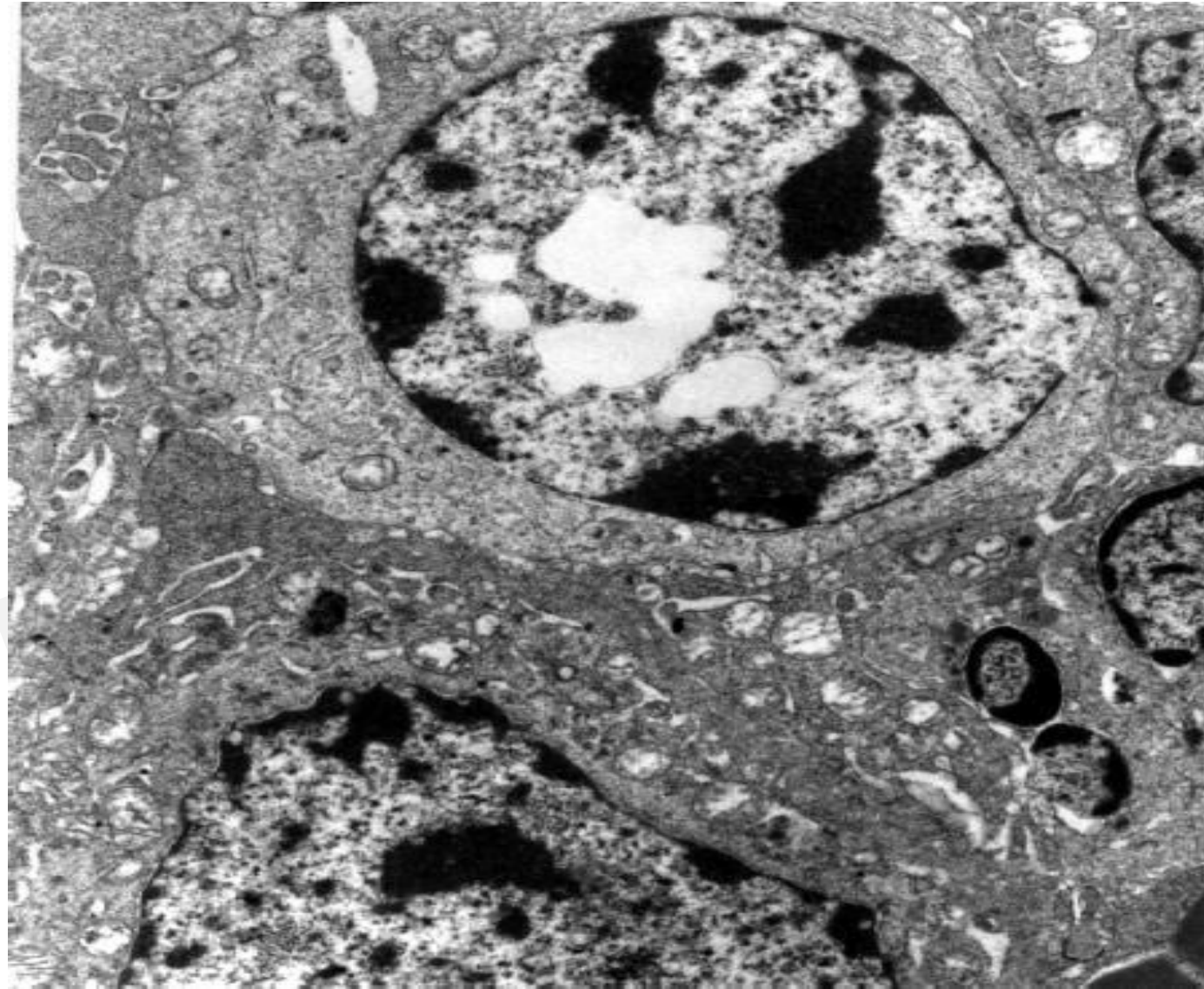
KARYORRHEXIS
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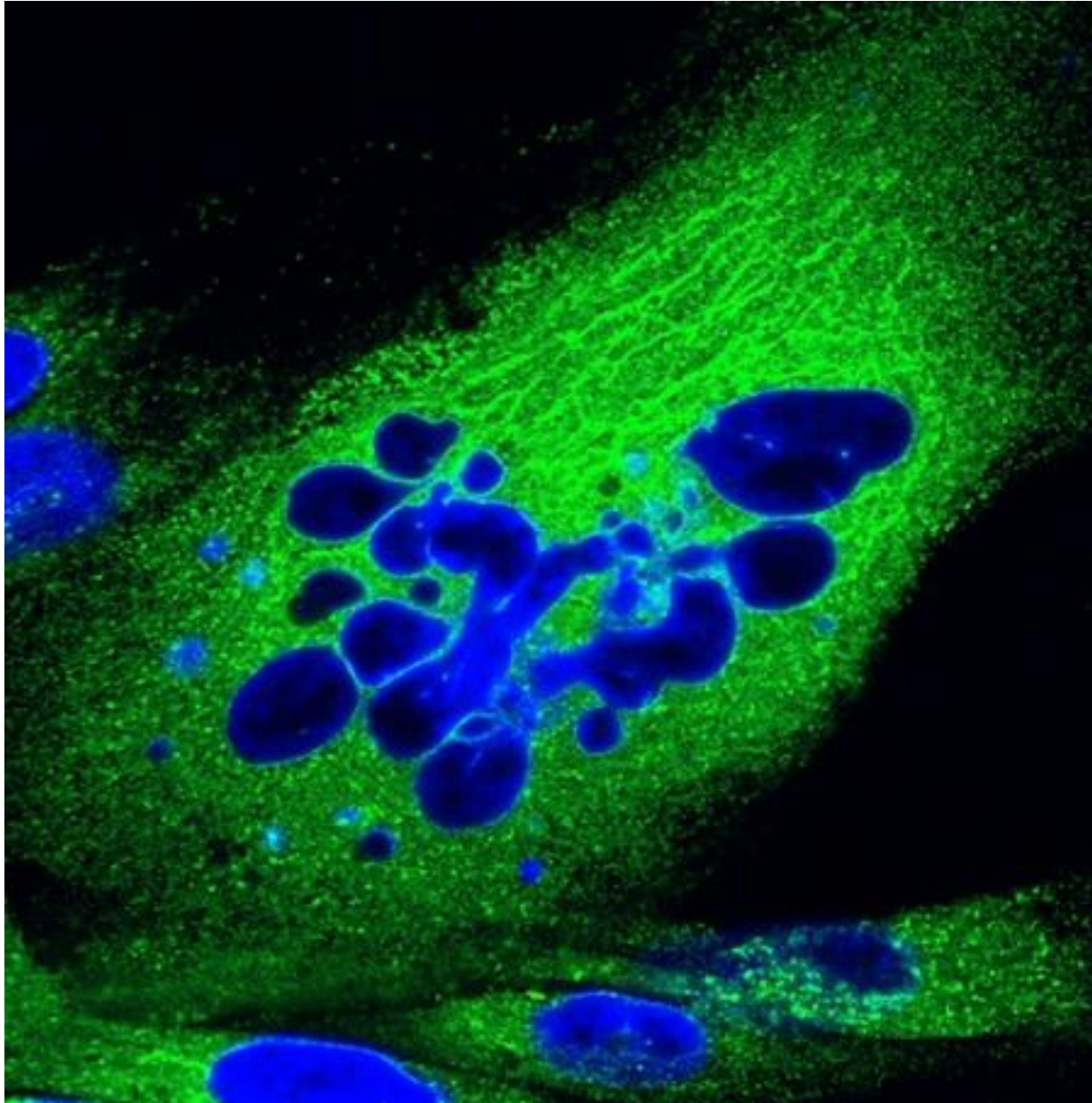




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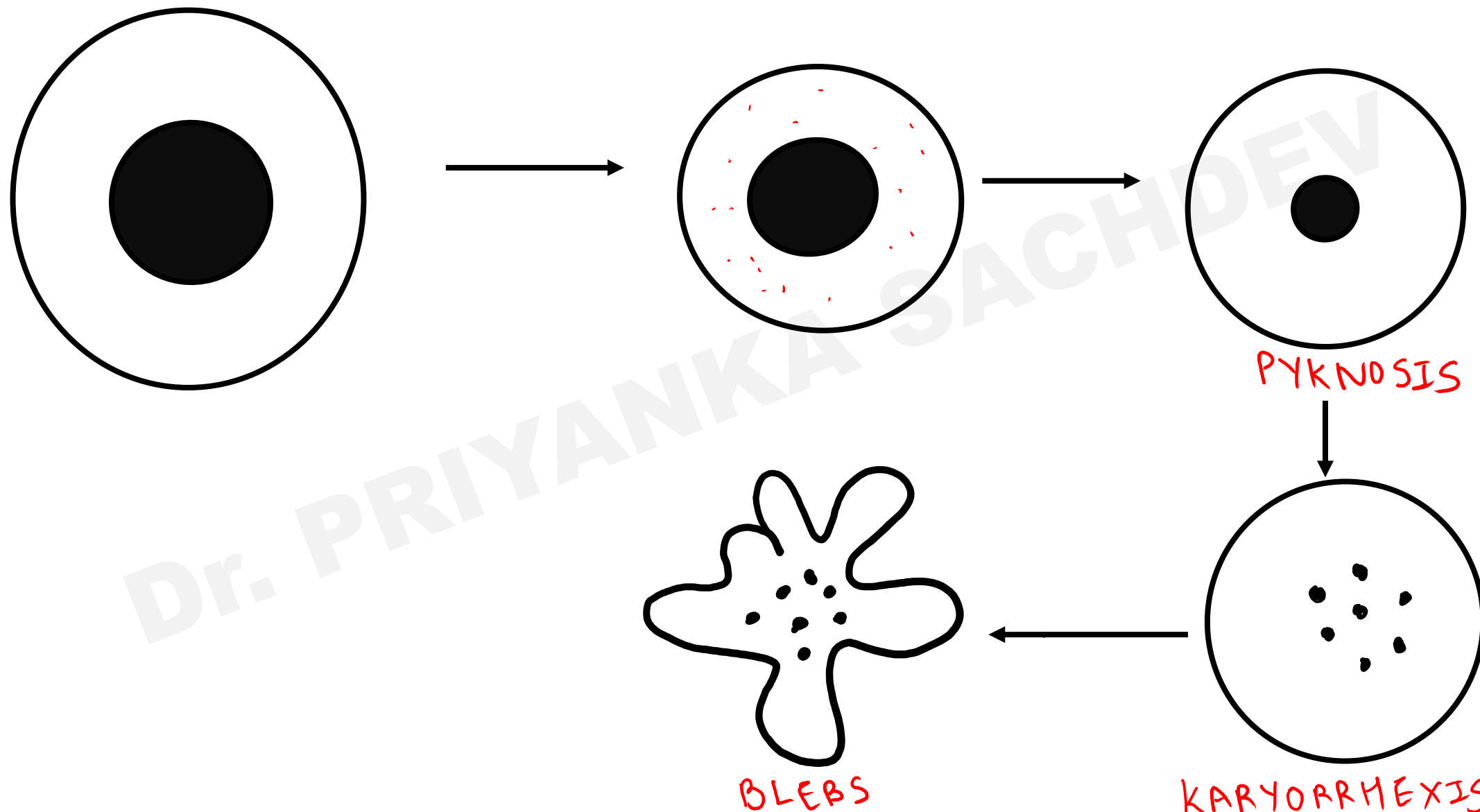
Dr. PRIYANKA SACHDEV



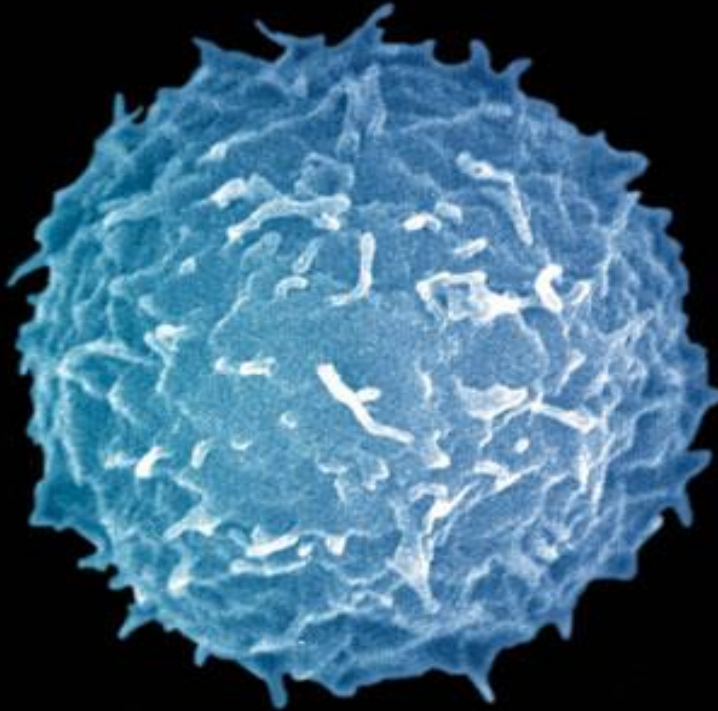
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4. Cytoplasmic membrane shows **multiple surface blebs.**

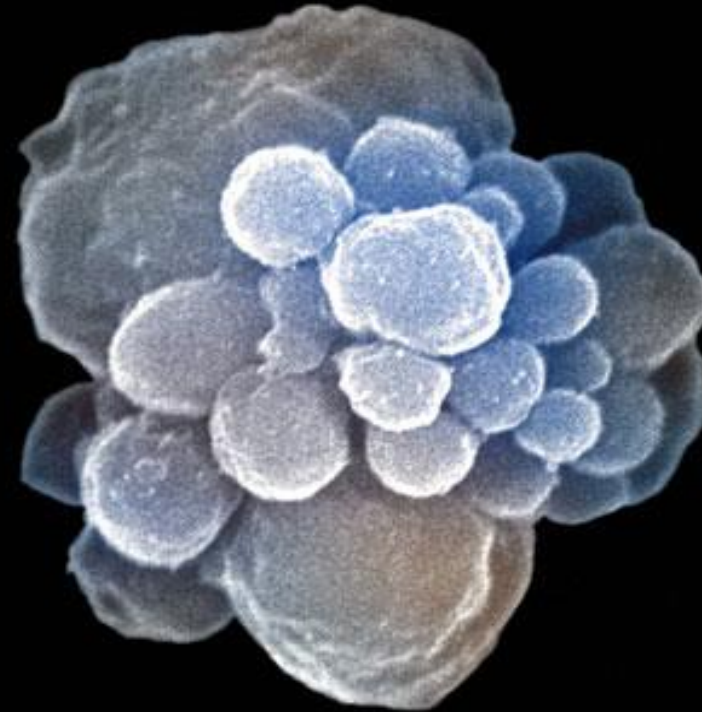
- It is the **end stage** of apoptosis.
- **Cell membrane intact** thus **preventing leaking out** of cellular contents.



normal WBC

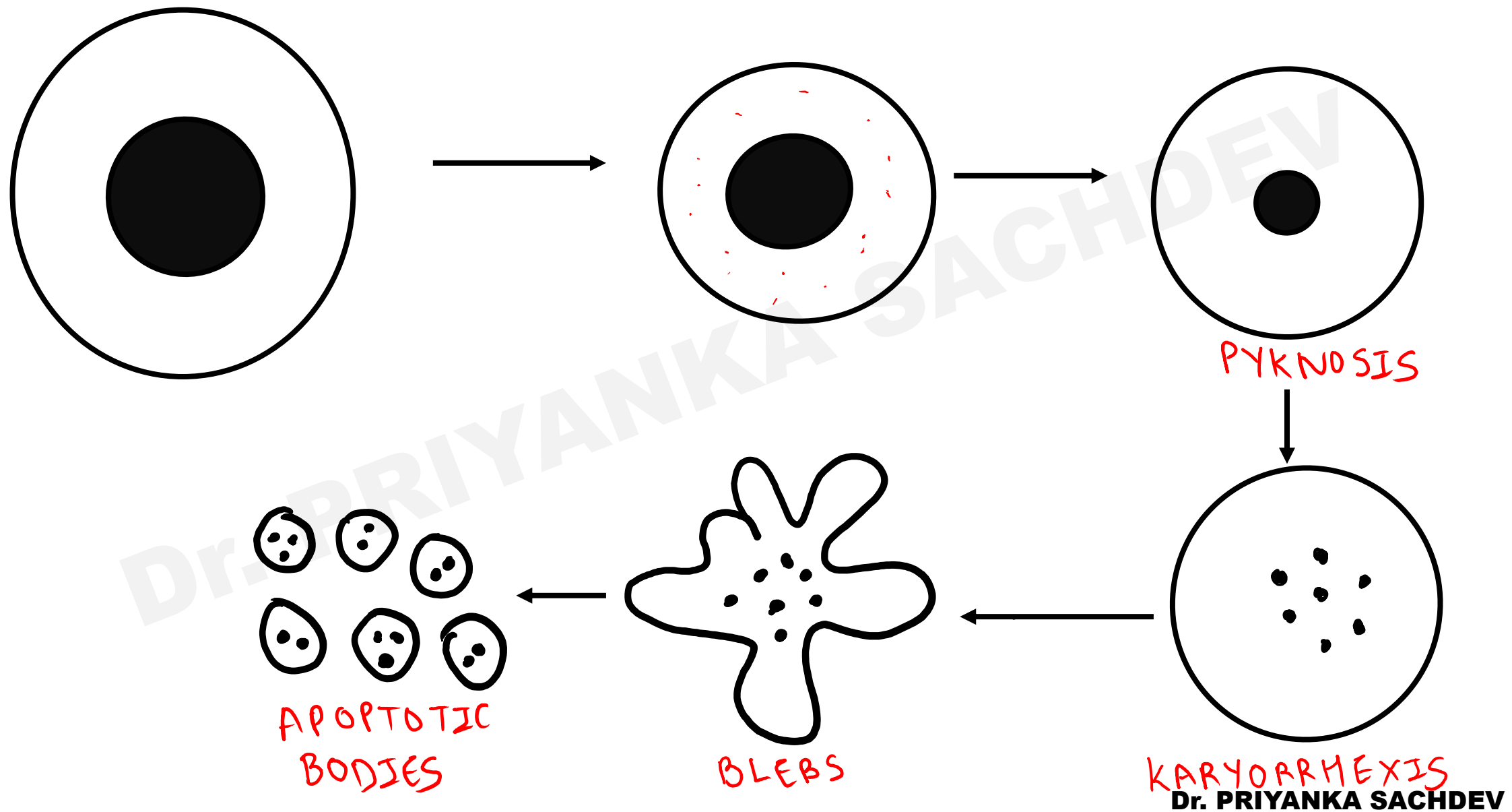


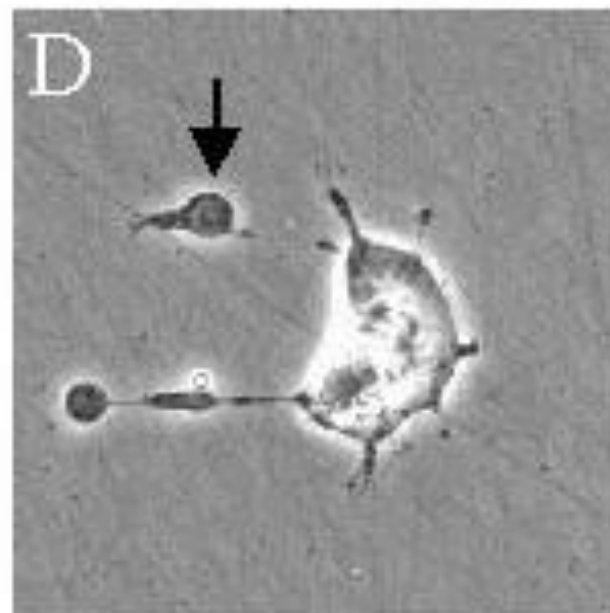
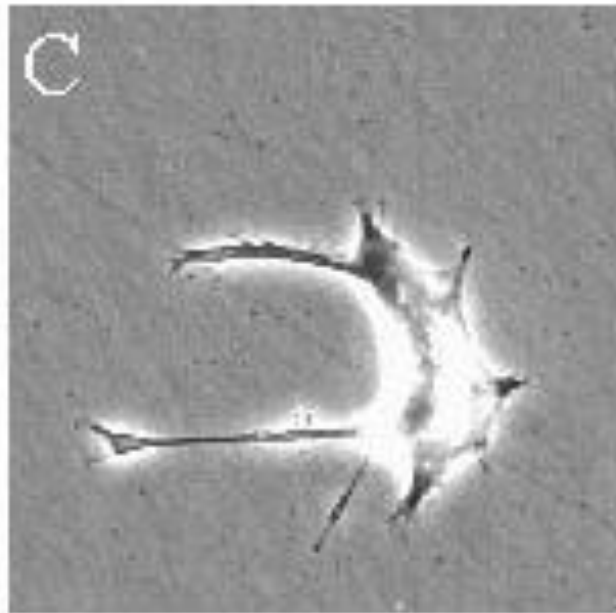
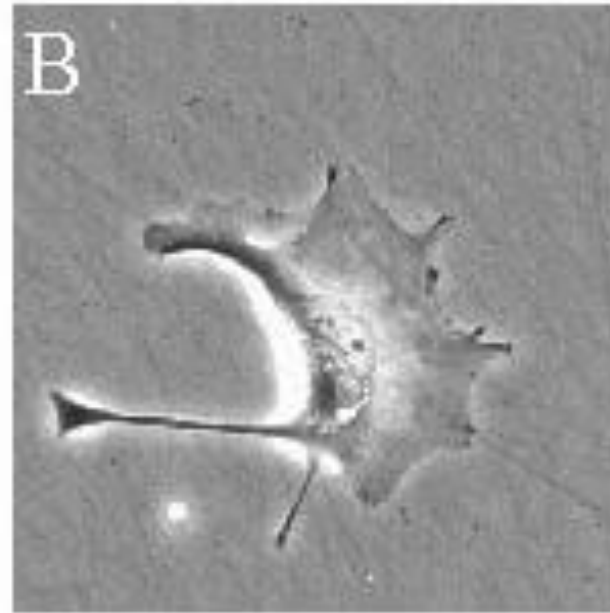
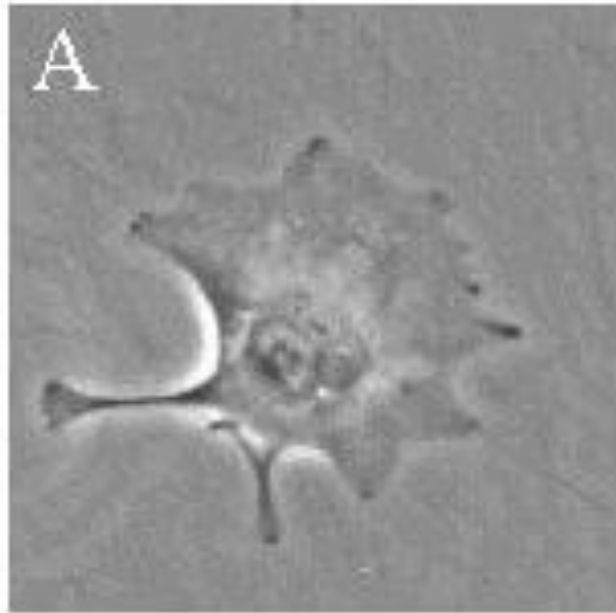
apoptotic WBC



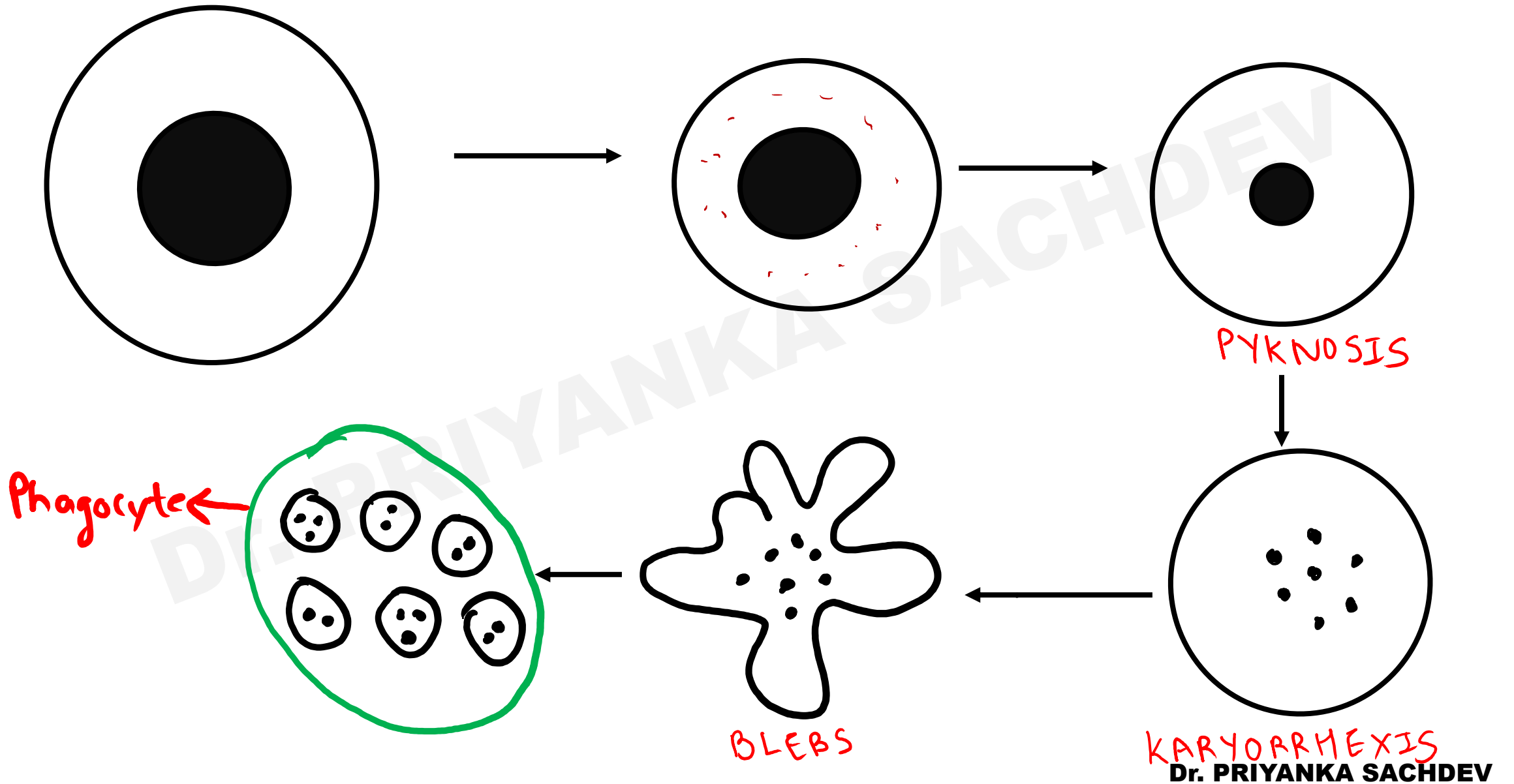
5. Nuclear fragments and cytoplasmic organelles form membrane bound **apoptotic bodies**

- These are membrane bound round masses of eosinophilic cytoplasm with tightly packed organelles which may contain nuclear debris





- These apoptotic bodies are recognised by **phagocytes** and **destroyed**
- Characteristically, unlike necrosis, there is **no acute inflammatory reaction** around apoptosis.



POLLS 3

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Cell Adaptation & Injury*



*Scan or Click to watch
Apoptosis & Necrosis*



*Scan or Click to watch
Inflammation*



*Scan or Click to watch
Haemodynamic Disorder*



The earliest change seen in apoptosis is

- **a) Cell shrinkage**
- **b) Pyknosis**
- **c) Formation of apoptotic bodies**
- **d) Fragmentation of cells**

The earliest change seen in apoptosis is

- **a) Cell shrinkage**
- b) Pyknosis
- c) Formation of apoptotic bodies
- d) Fragmentation of cells

Characteristic feature of apoptosis

- a) Cell membrane intact
- b) Cytoplasmic Basophilia
- c) Nuclear moulding
- d) Cell swelling

Characteristic feature of apoptosis

- a) Cell membrane intact
- b) Cytoplasmic Basophilia
- c) Nuclear moulding
- d) Cell swelling

All of the following are features of apoptosis EXCEPT

- a) Cellular swelling
- b) Nuclear compaction
- c) Intact cell membrane
- d) Cytoplasmic eosinophilia

All of the following are features of apoptosis EXCEPT

- **a) Cellular swelling**
- **b) Nuclear compaction**
- **c) Intact cell membrane**
- **d) Cytoplasmic eosinophilia**

Apoptotic bodies are

- a) Clumped chromatin bodies
- b) Pyknotic nucleus without organelles
- c) Cell membrane bound with organelles
- d) No nucleus with organelles

Apoptotic bodies are

- a) Clumped chromatin bodies
- b) Pyknotic nucleus without organelles
- c) Cell membrane bound with organelles
- d) No nucleus with organelles

True about Apoptosis are all except-

- a) Inflammation is present
- b) Chromosomal brekage
- c) Clumping of chromatin
- d) Cell shrinkage

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A

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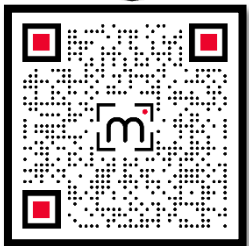
OVERVIEW

- **Definition**
- **Types**
- **Mechanisms**
- **Morphological changes in apoptosis**
- **Diagnosis of Apoptosis**
- **Differences from necrosis**

DIAGNOSIS OF APOPTOSIS

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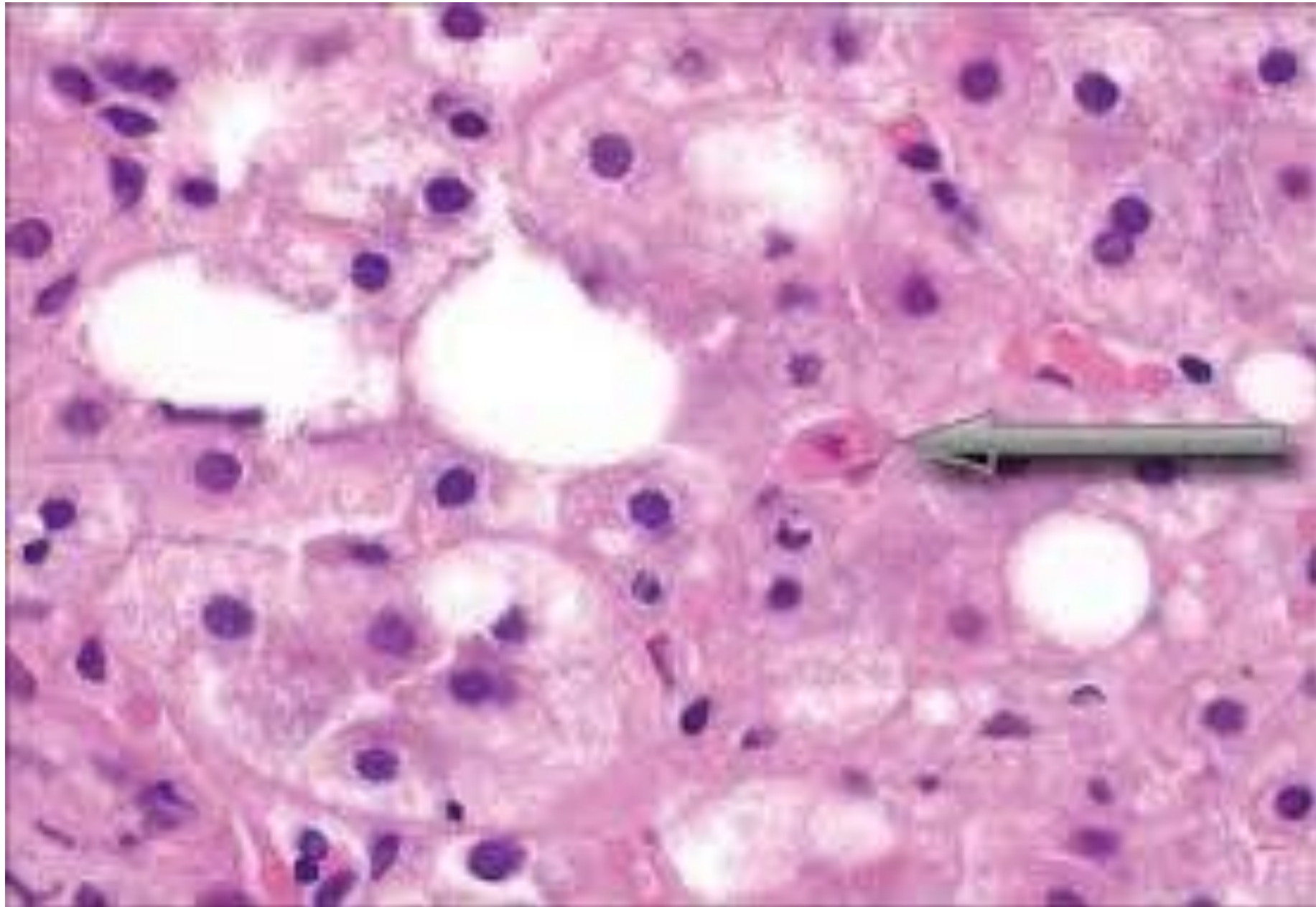


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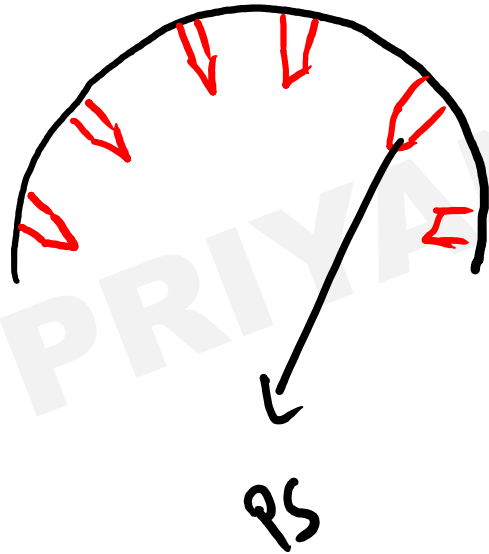


1. Apoptosis markers

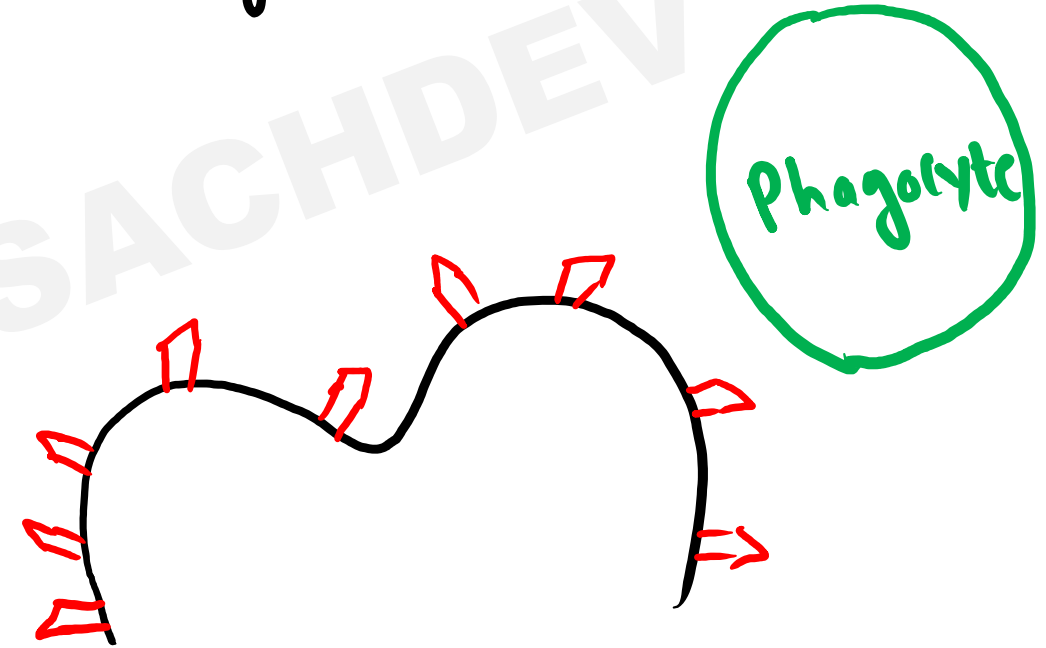
- **Annexin-V** is a recombinant protein with high affinity for phospholipid like phosphatidylserine.
- Phosphatidylserine is a phospholipid present on inner surface membrane normally but it is flipped to outer surface during apoptosis thus become a marker of apoptosis.



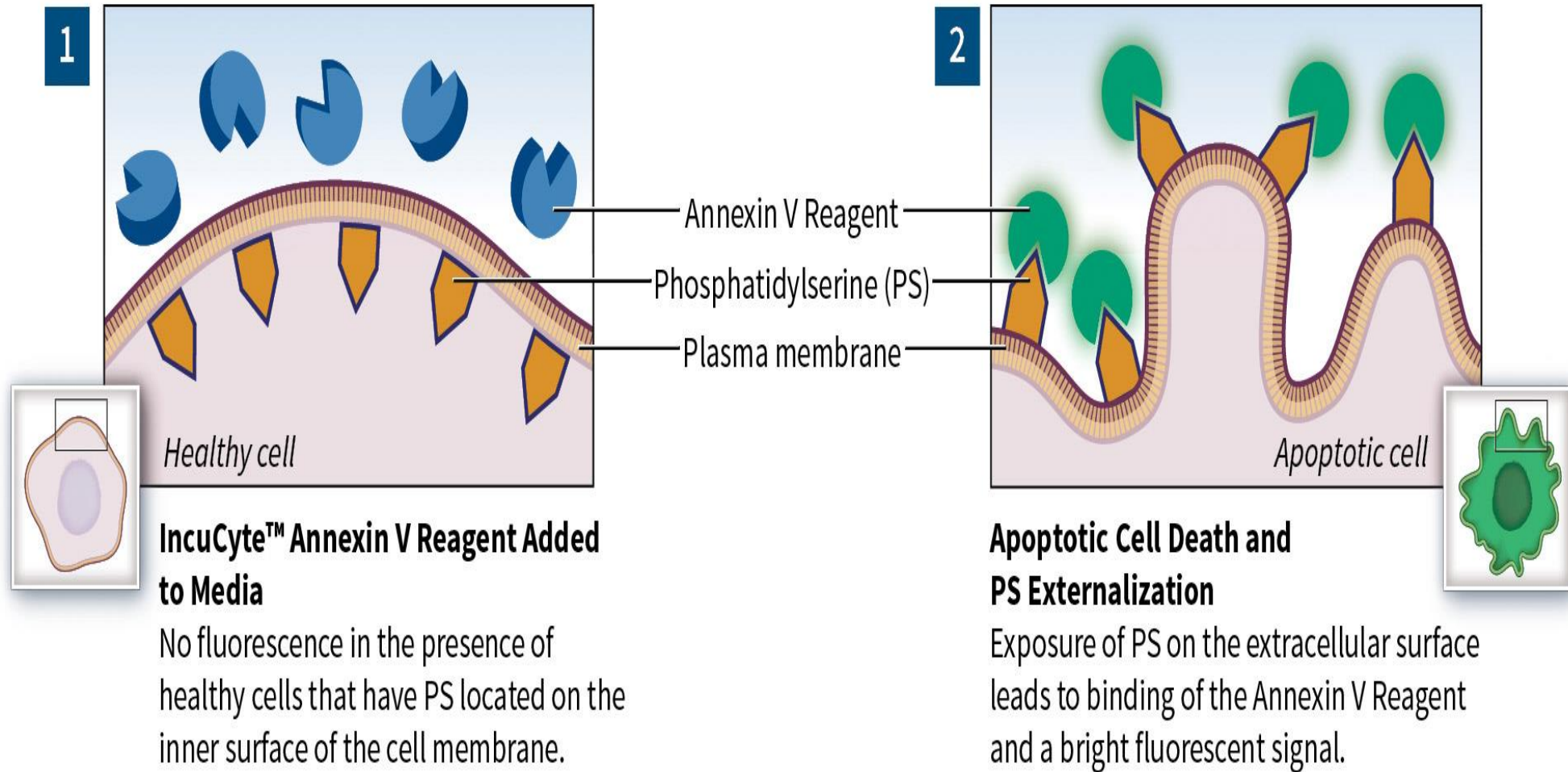
Normally



During apoptosis



Annexin V overview schematic



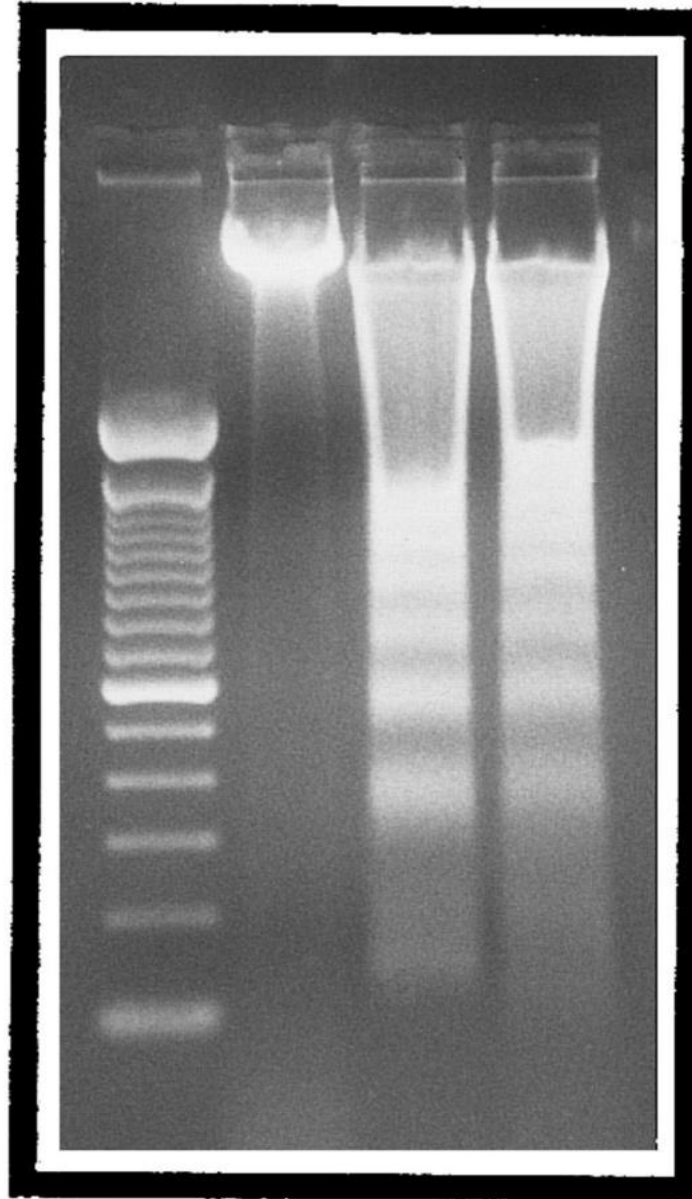
2. Agarose gel electrophoresis:

- Fragmented DNA shows **Step Ladder Pattern**, which is due to internucleosomal cleavage of DNA by endonuclease
- During karyorrhexis **endonuclease** activation leaves short DNA fragments regularly spaced in size.
- This ladder pattern is **characteristic but not specific** for apoptosis.

M 1 2 3

1.5 kb →

0.6 kb →



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POLLS 4

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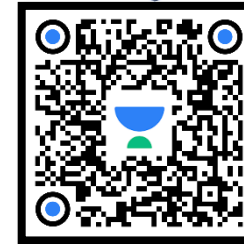
*Scan or Click to watch
Apoptosis & Necrosis*



*Scan or Click to watch
Inflammation*



*Scan or Click to watch
Haemodynamic Disorder*



Ladder pattern of DNA electrophoresis in apoptosis is caused by the action of the following enzyme

- a) Endonuclease
- b) Transglutaminase
- c) DNase
- d) Caspase

Ladder pattern of DNA electrophoresis in apoptosis is caused by the action of the following enzyme

- **a) Endonuclease**
- b) Transglutaminase
- c) DNase
- d) Caspase

Annexin V is a marker of-

- **a) Apoptosis**
- **b) Necrosis**
- **c) Artherosclerosis**
- **d) Inflammation**

Annexin V is a marker of-

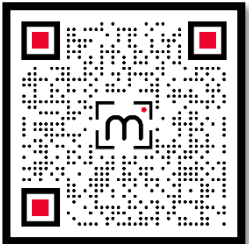
- **a) Apoptosis**
- **b) Necrosis**
- **c) Artherosclerosis**
- **d) Inflammation**

OVERVIEW

- Definition
- Types
- Mechanisms
- Morphological changes in apoptosis
- Diagnosis of Apoptosis
- Differences from necrosis

Differences from necrosis

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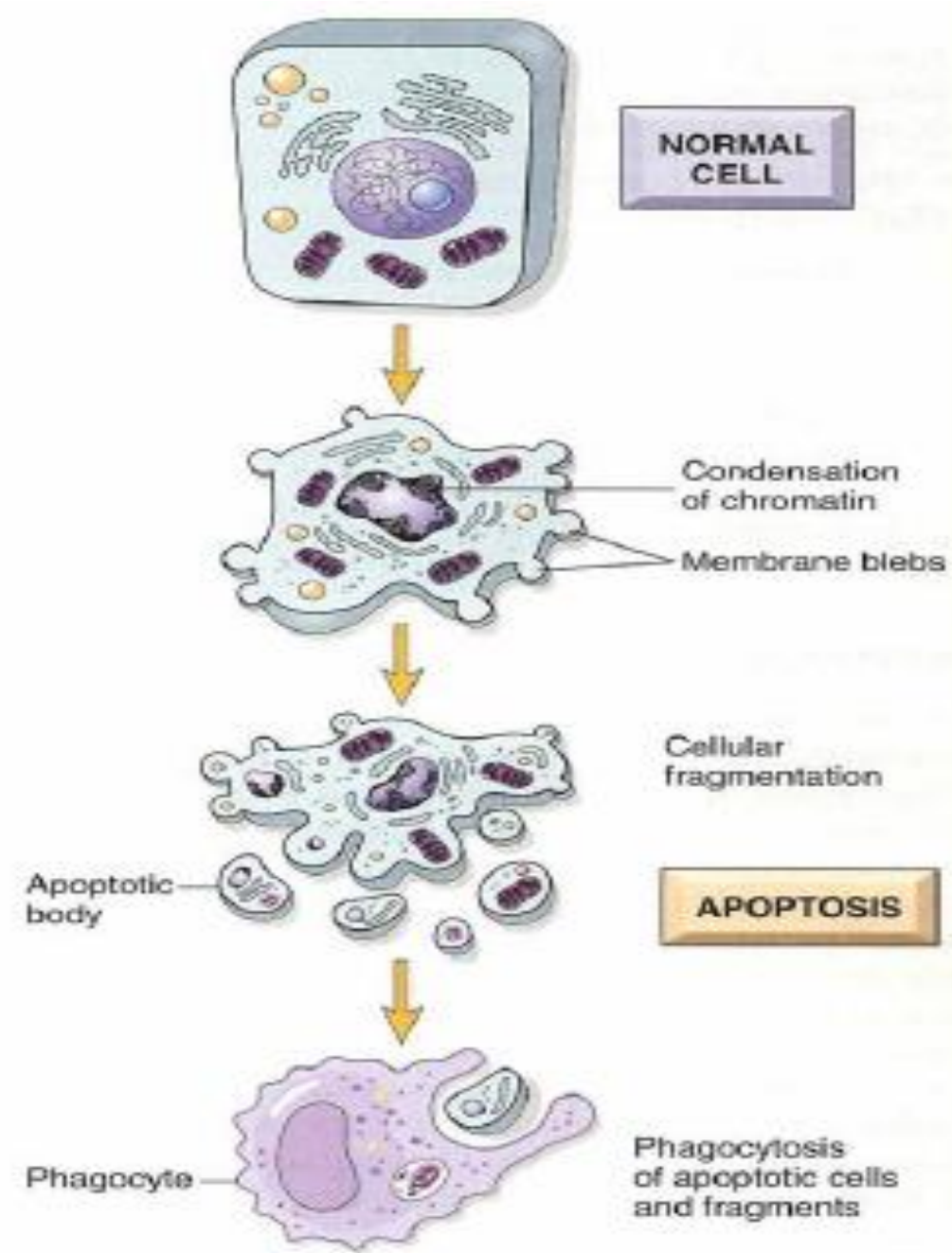
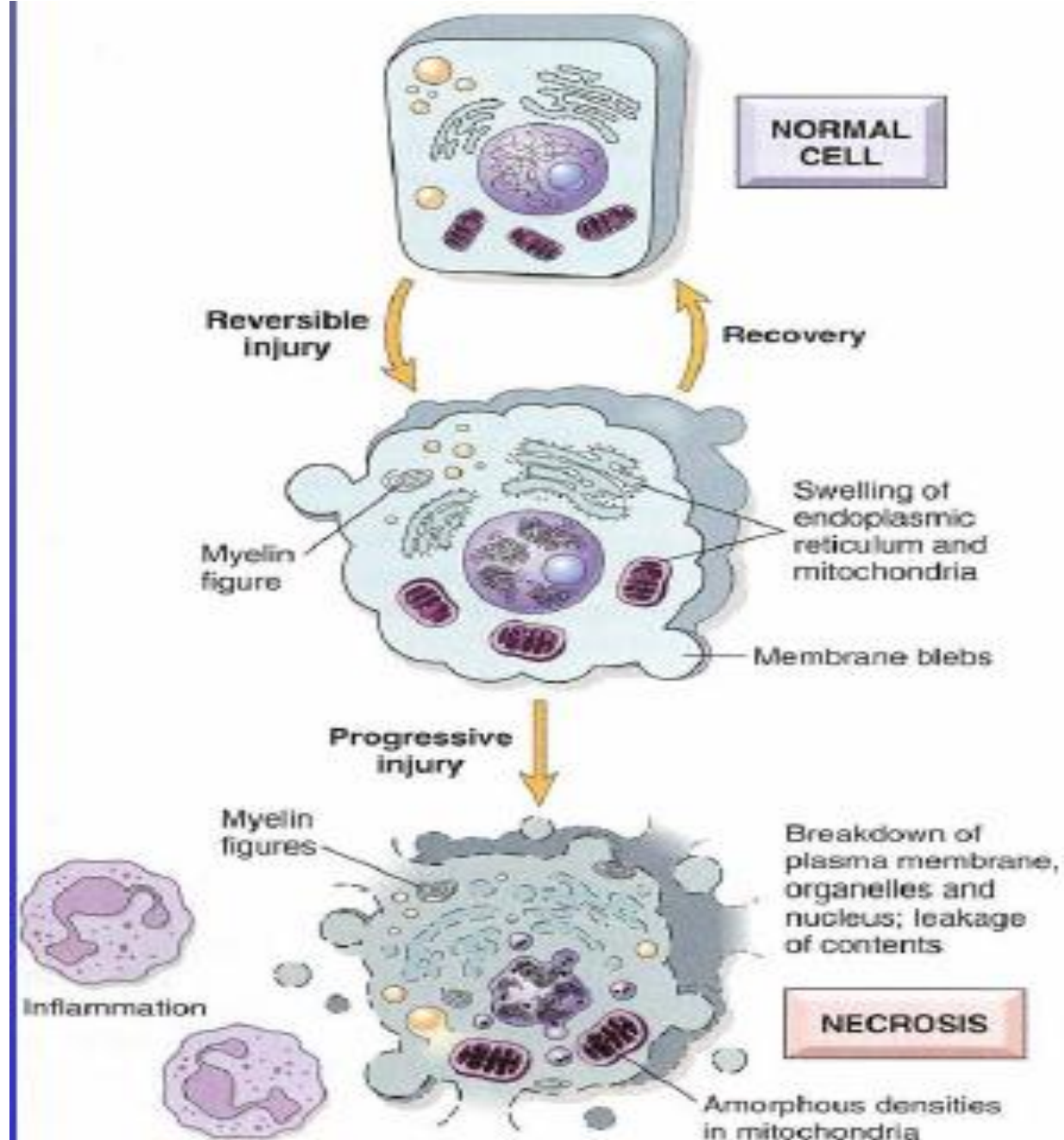
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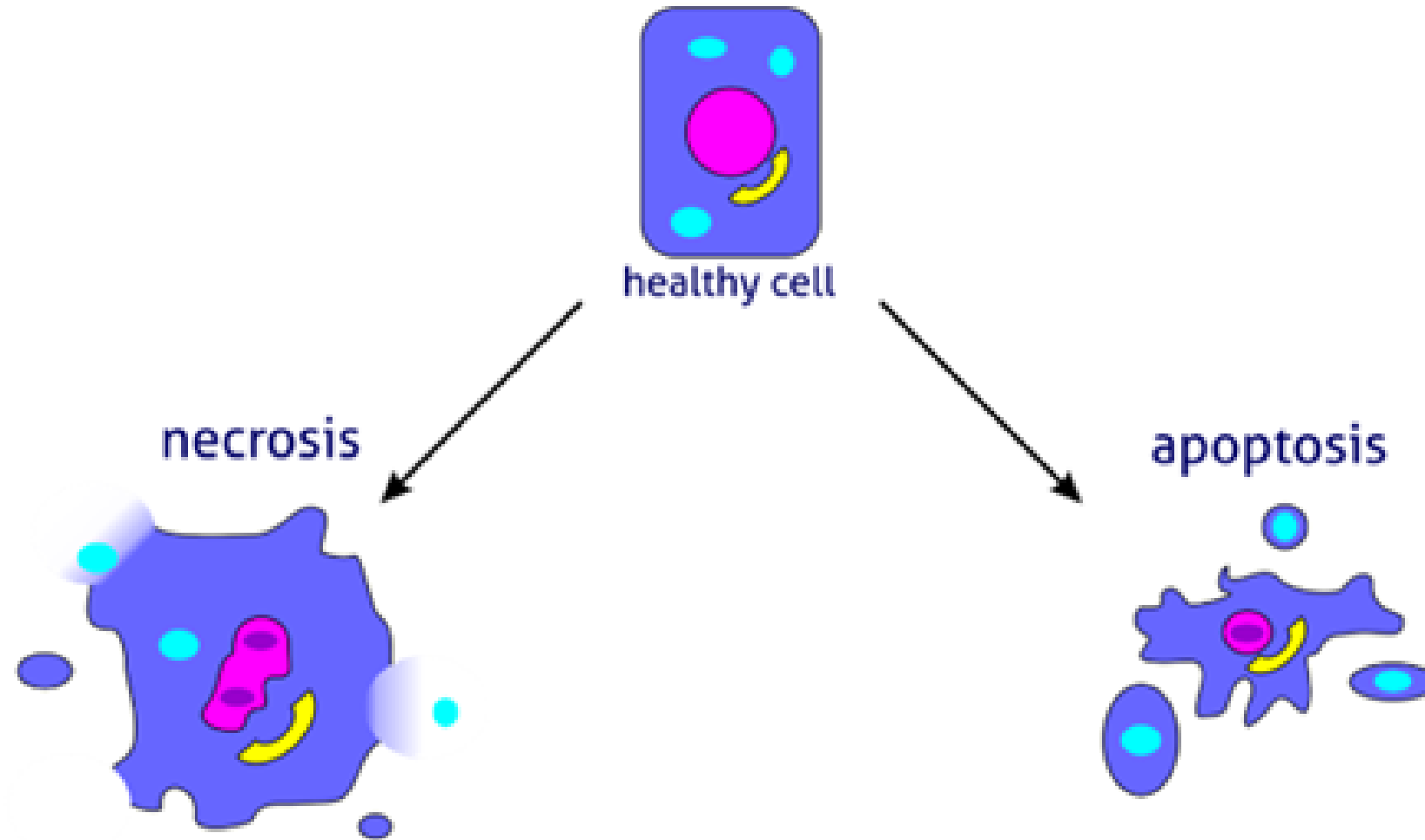
Apoptosis

Single cells or small clusters of cells
Cell shrinkage and convolution
Pyknosis and karyorrhexis
Intact cell membrane
Cytoplasm retained in apoptotic bodies
No inflammation

Necrosis

Often contiguous cells
Cell swelling
Karyolysis, pyknosis, and karyorrhexis
Disrupted cell membrane
Cytoplasm released
Inflammation usually present





healthy cell

necrosis

apoptosis

- increase in cell volume
- loss of plasma membrane integrity
- leakage of cellular contents

- cell shrinkage
- plasma membrane blebbing
- formation of apoptotic bodies

POLLS 5

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Cell Adaptation & Injury*



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Apoptosis & Necrosis*



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Inflammation*



*Scan or Click to watch
Haemodynamic Disorder*



What is the common change in cell death associated with both apoptosis and necrosis?

- a) Cell shrinkage
- b) Bleb formation
- c) Chromatin condensation
- d) Presence of inflammation

What is the common change in cell death associated with both apoptosis and necrosis?

- a) Cell shrinkage
- b) Bleb formation
- **c) Chromatin condensation**
- d) Presence of inflammation

Apoptosis is differentiated from necrosis by presence of following feature

- a) Absence of inflammation
- b) Cell swelling
- c) Disruption of plasma membrane
- d) Passive process

Apoptosis is differentiated from necrosis by presence of following feature

- **a) Absence of inflammation**
- b) Cell swelling
- c) Disruption of plasma membrane
- d) Passive process

CELL DEATH



- Apoptosis
- Necrosis

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NECROSIS

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Cell Adaptation & Injury*



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Apoptosis & Necrosis*



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Inflammation*



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Haemodynamic Disorder*



Normally cells in homeostasis



Physiological and pathological stress



Cellular adaptation (reversible on withdrawal of stimulus)



If the irritant stimulus persists for long time



Cell injury



Reversible cell injury



Irreversible cell injury (Cell death)

-Apoptosis

-Necrosis

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DEFINITION

- Necrosis is **death of cells and tissues in the living animal**
- Necrosis is defined as a **localised area of death of tissue followed later by degradation of tissue by hydrolytic enzymes liberated from dead cells**
- It is invariably accompanied by **inflammatory reaction**

REMEMBER

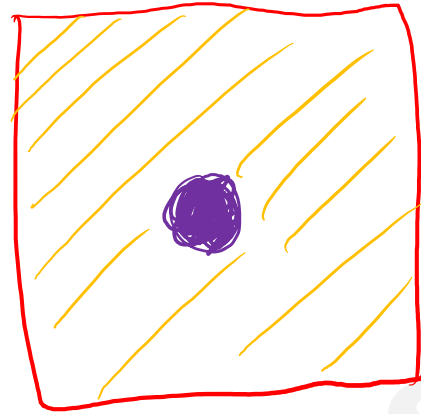
- Necrosis usually affects **a group of contiguous cells** (in contrast to apoptosis which involves a single cell).
- There are **inflammatory changes** in the surrounding tissue (in contrast to apoptosis where there is no inflammatory changes).

Types of Necrosis (CCCCFF)

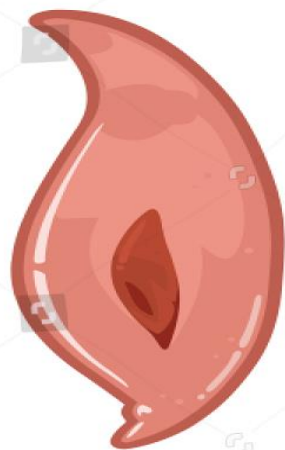
- 5 types→

- Coagulative necrosis (most common)
- Colliquative / Liquefactive necrosis
- Caseous
- Fat necrosis
- Fibrinoid necrosis

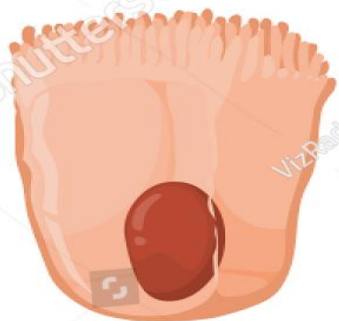
- **Introduction**
- **Causes**
- **Gross**
- **Microscopy**



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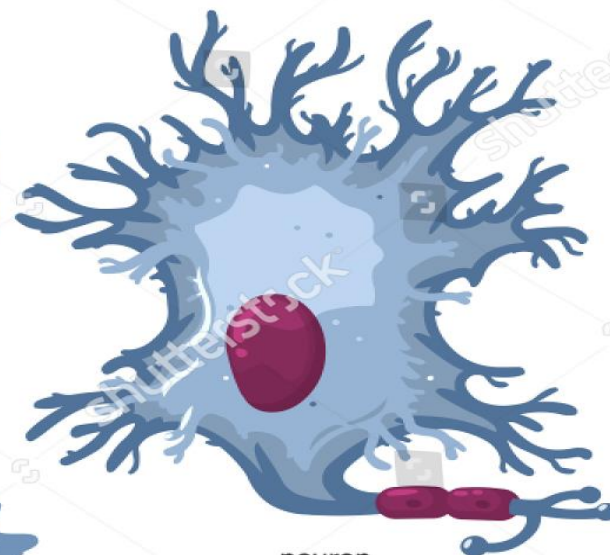
muscle cell



intestinal cell



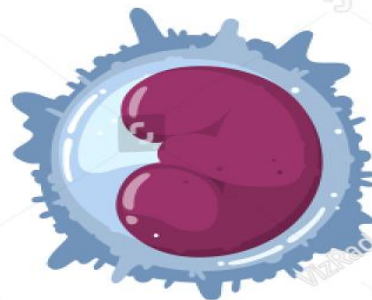
fat cell



neuron



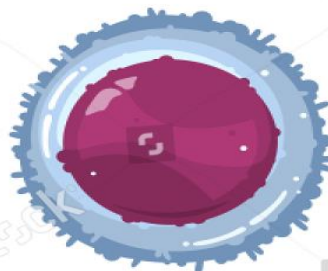
red blood cell



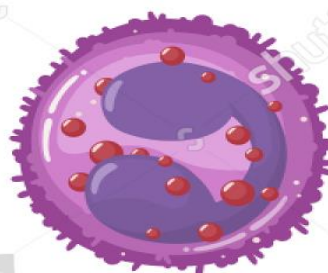
monocyte



basophil



limphocyte



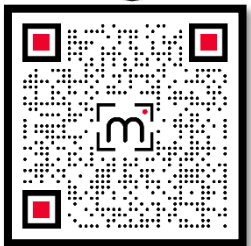
eosinophil



neutrophil

Coagulative necrosis

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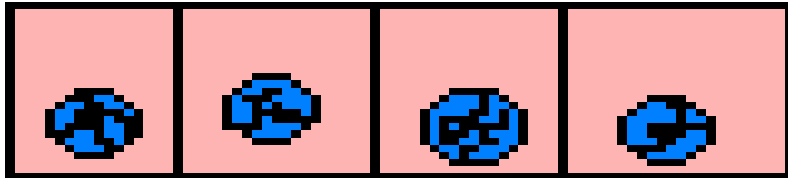


- **Introduction**
- **Causes**
- **Gross**
- **Microscopy**

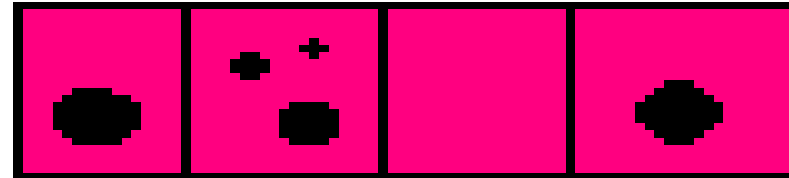
INTRODUCTION

- **Most common** type of necrosis
- **Architectural outlines persist but cellular and nuclear details are lost (Ghost cells)**
- Type of tissue can be **recognized**
- Denaturation (coagulation) of structural and enzymic proteins blocks proteolysis.

Alive



Coagulation Necrosis



Causes:

- 1. Ischemia** due to thrombosis/ embolism **in all organs except brain** (Amongst solid organs brain is the only exception, i.e., it is the only solid organ in which ischemia leads to liquefactive necrosis and not coagulative necrosis)
2. Mild burns (thermal injury)
3. Zenker's degeneration necrosis

Grossly

- Focus in the early stage is **pale, firm, and slightly swollen**
- With progression, the affected area becomes **more yellowish, softer, and shrunken.**



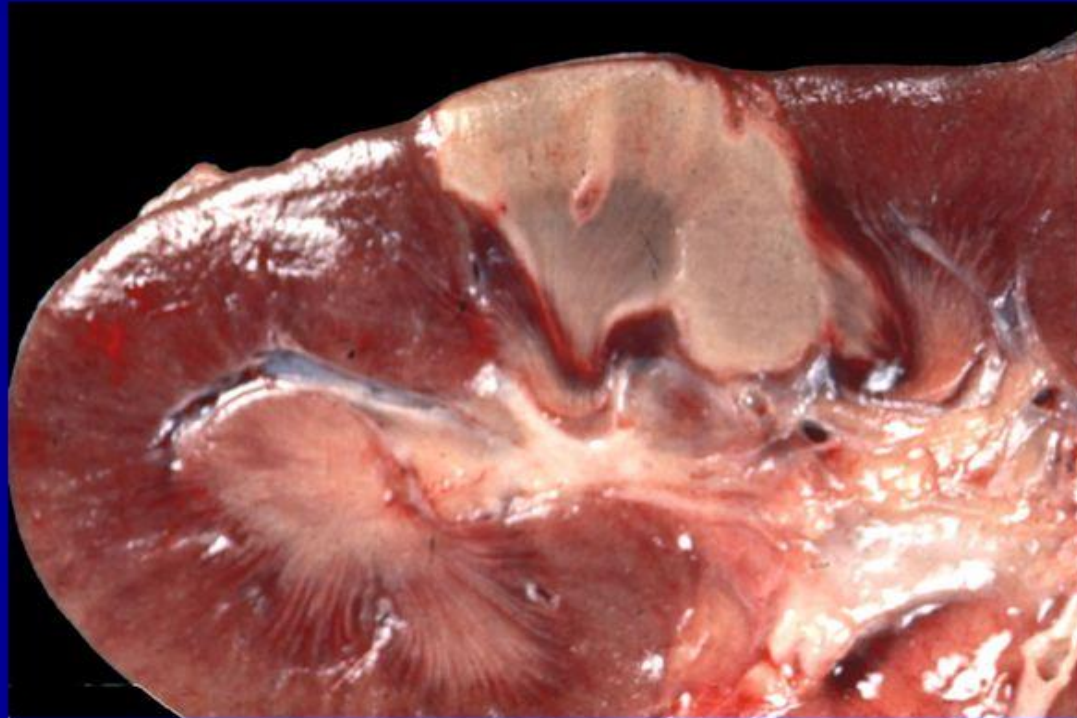
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Coagulative Necrosis

Kidney - Gross



Microscopically

- The hallmark of coagulative necrosis is the conversion of normal cells into their '**tomb stones**' i.e. **outlines of the cells are retained and the cell type can still be recognised but their cytoplasmic and nuclear details are lost**

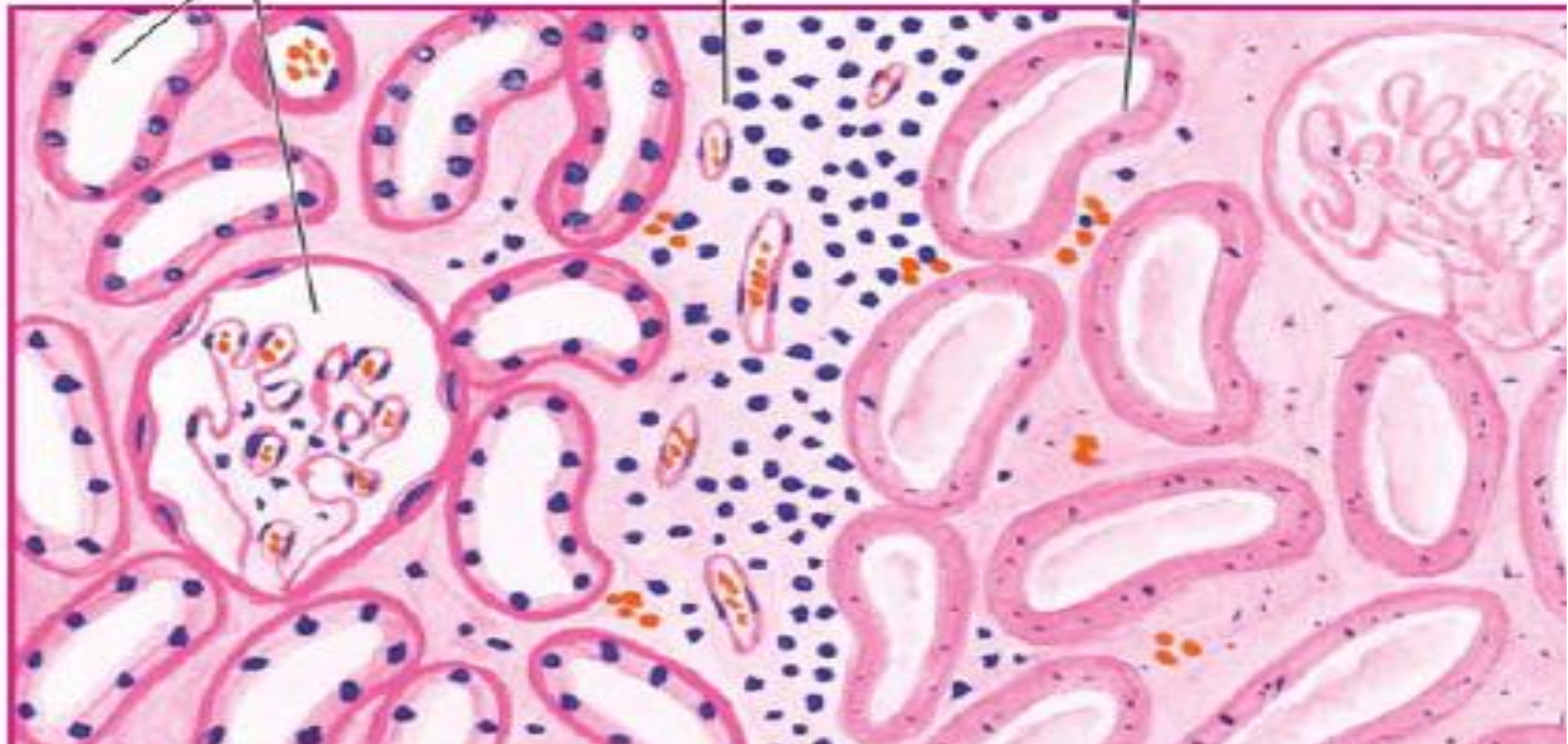


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Viable renal tissue

Inflammatory
cell infiltrate

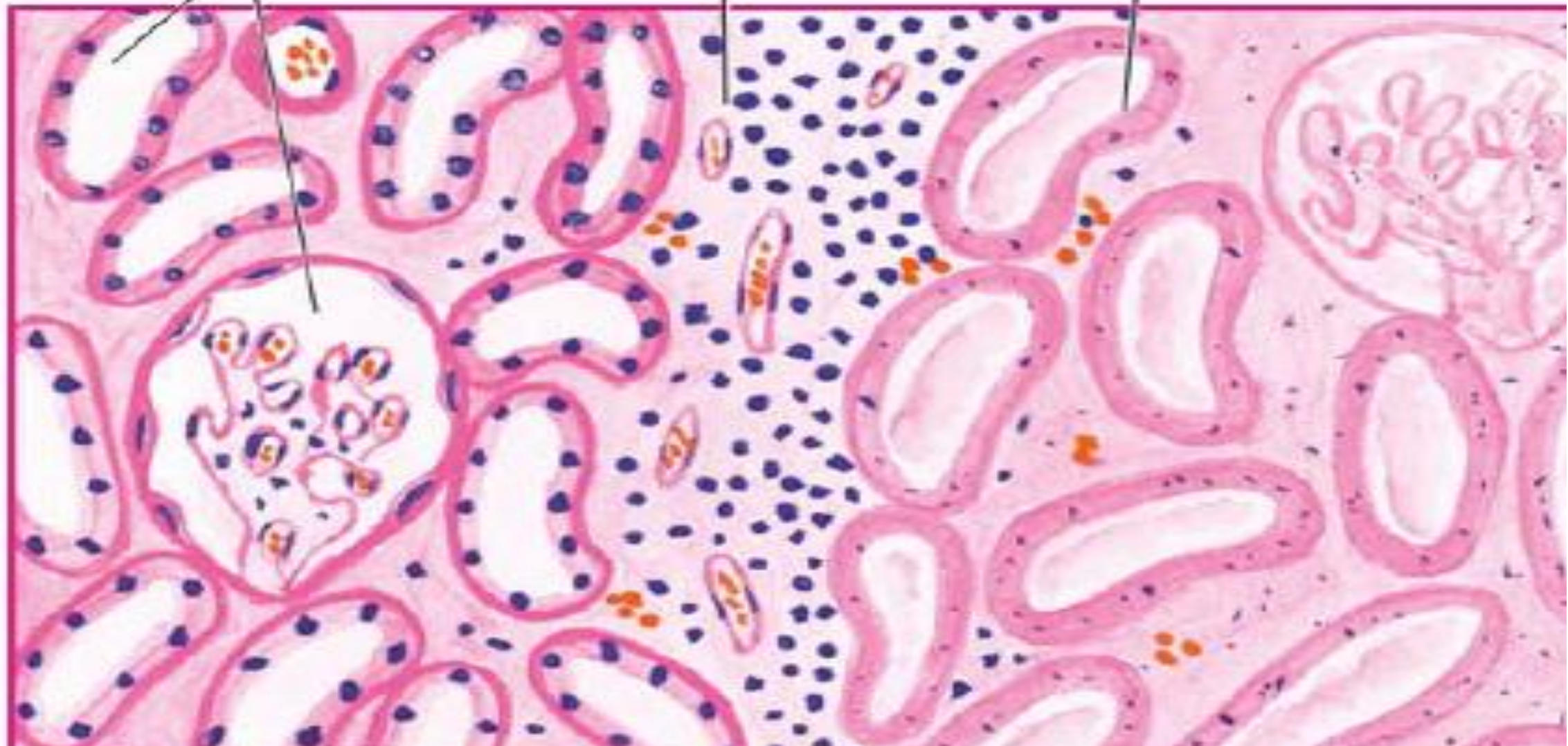
Necrotic tissue



Viable renal tissue

Inflammatory
cell infiltrate

Necrotic tissue

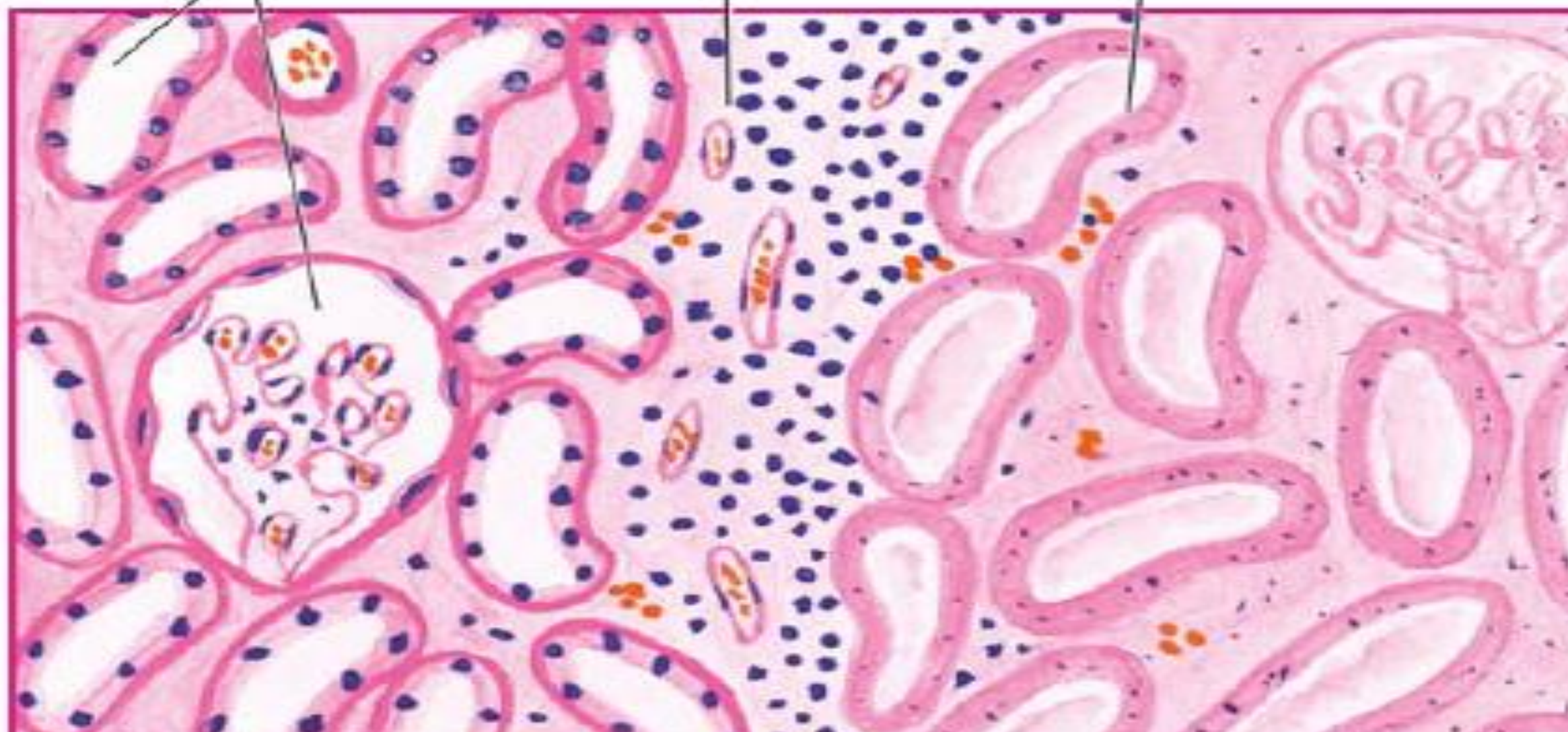


1. **'Tomb stones'** i.e. outlines of the cells are retained and the cell type can still be recognised but their cytoplasmic and nuclear details are lost
2. The necrosed cells are **swollen and have more eosinophilic cytoplasm** than the normal.
3. These cells show **nuclear changes of pyknosis, karyorrhexis and karyolysis**
4. Eventually, the necrosed focus is infiltrated by **inflammatory cells**

Viable renal tissue

Inflammatory
cell infiltrate

Necrotic tissue

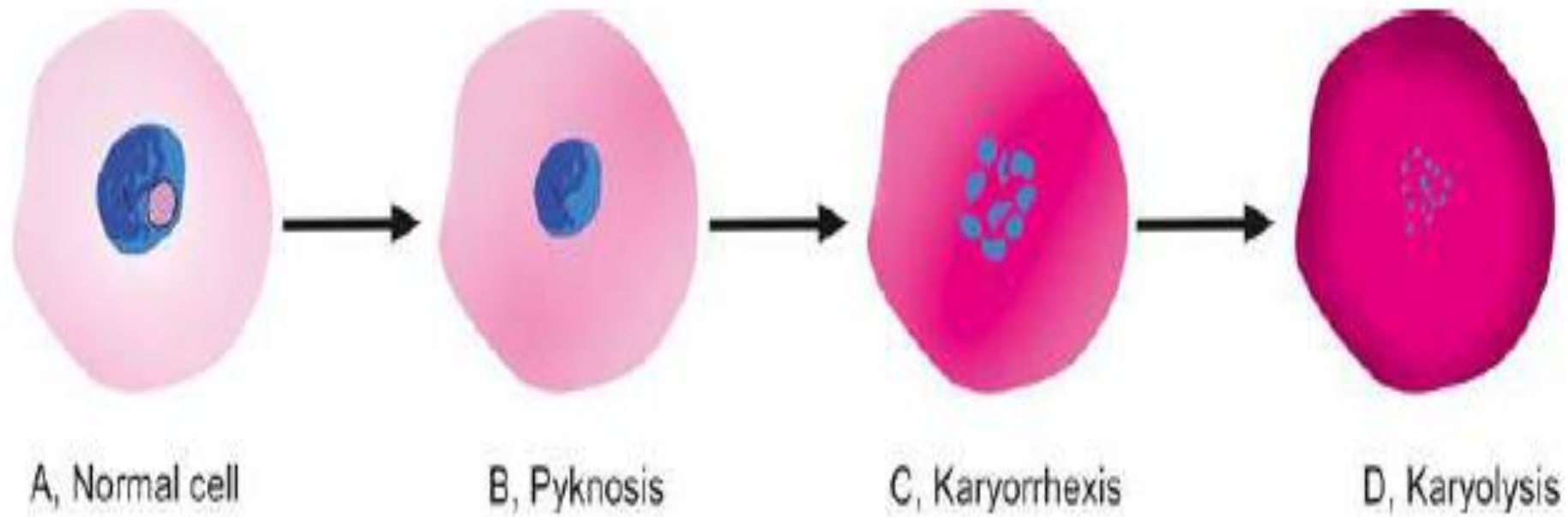


Viable renal tissue

Inflammatory
cell infiltrate

Necrotic tissue





	COAGULATIVE	LIQUIDFACTIVE	CASSEOUS	FIBRINOID	FAT
INTRO					
CAUSES					
GROSS					
MICRO					

Types of Necrosis (CCCCFF)

- 5 types→

- Coagulative necrosis (most common)
- Colliquative / Liquefactive necrosis
- Caseous
- Fat necrosis
- Fibrinoid necrosis

Liquefactive (COLLIQUATIVE) necrosis

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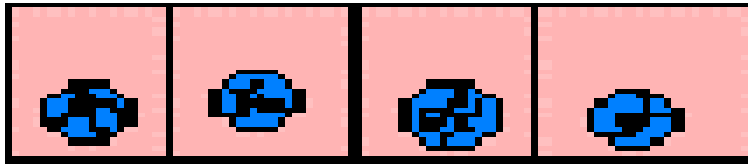
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- **Introduction**
- **Causes**
- **Gross**
- **Microscopy**

INTRODUCTION

- Liquefaction or colliquative necrosis → hydrolytic enzymes in tissue degradation have a dominant role in causing **semi-fluid material**
- **Their architectural details as well as cytoplasmic and nuclear details are lost**

Alive

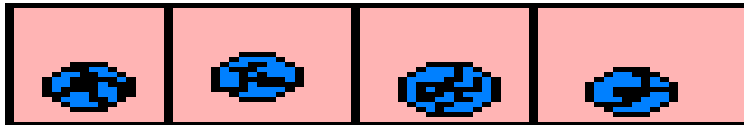


Liquefaction Necrosis

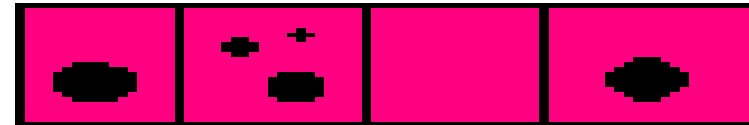


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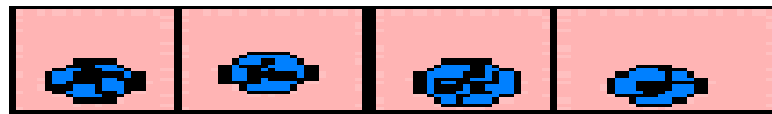
Alive



**Coagulation
Necrosis**



Alive



**Liquefaction
Necrosis**

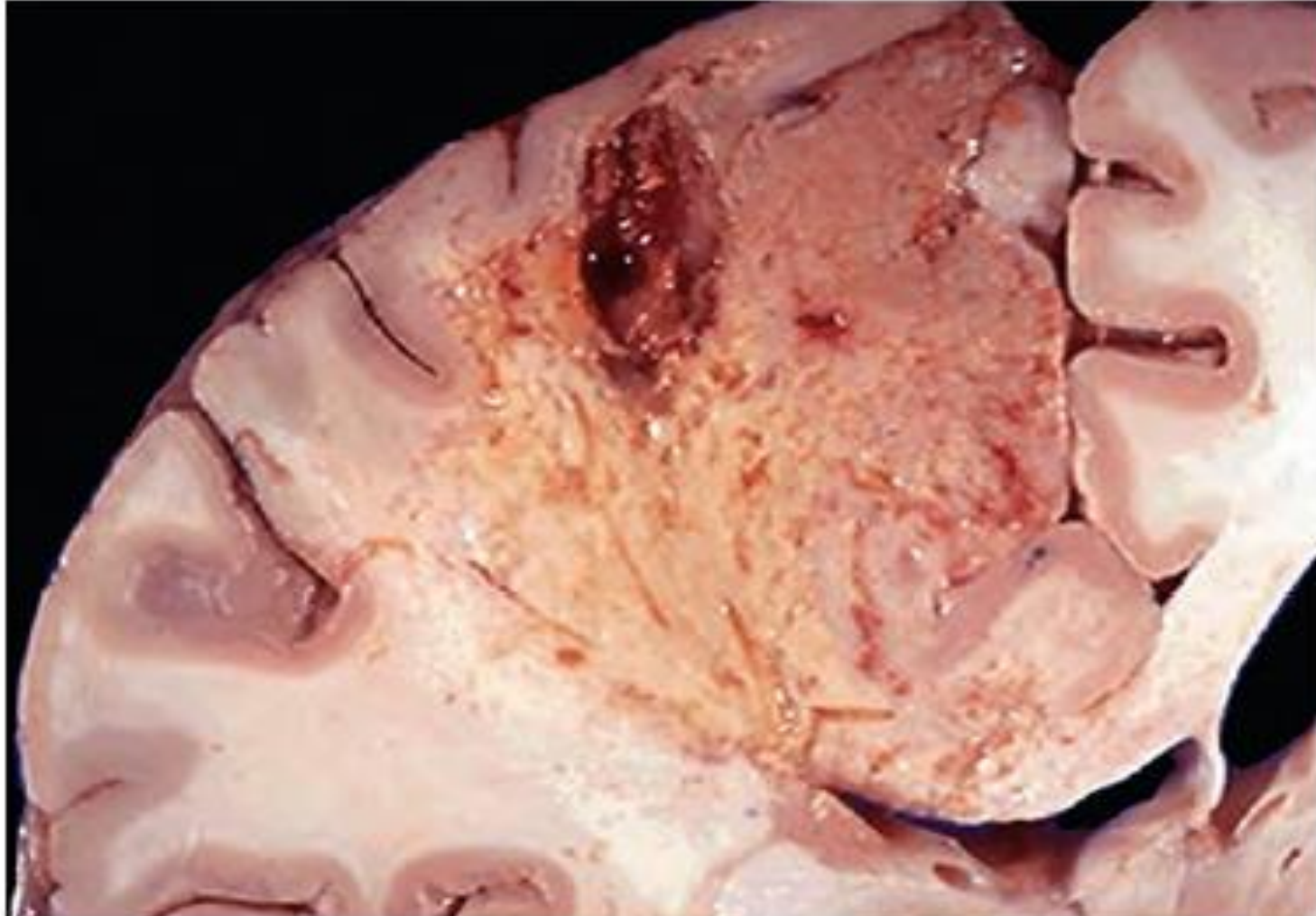


Causes:

1. **Pyogenic bacterial infections** attract neutrophils. Bacterial and leukocytic enzymes liquefy dead cells and tissues.
2. **Ischemic necrosis of brain**

Gross appearance

- Affected area is **soft with liquefied centre containing necrotic debris**
- Later, a **cyst wall** is formed.



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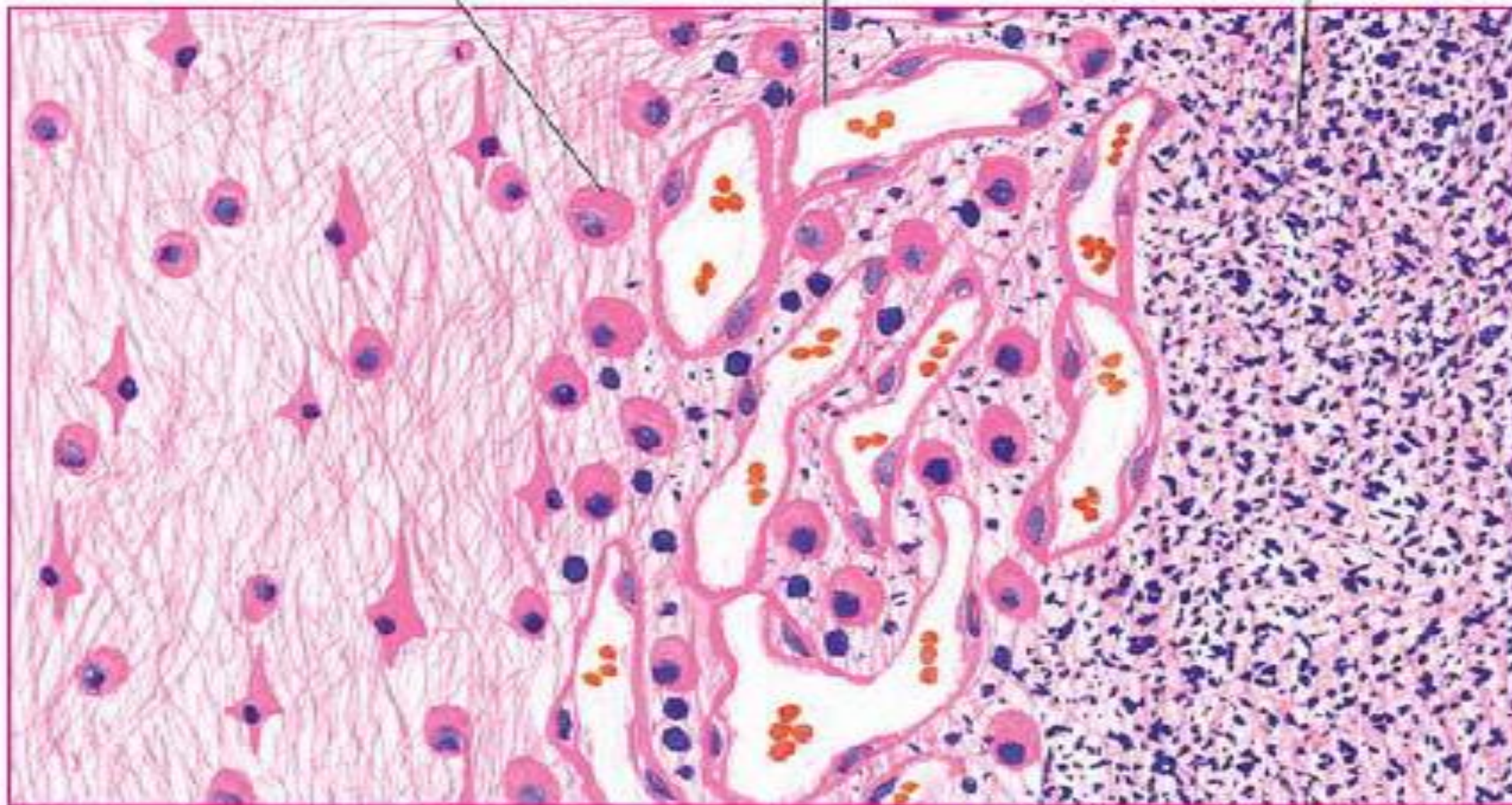
Microscopic appearance:

1. No architectural or cellular details are visible in the area of necrosis.
2. The necrotic area usually appears as a cavity containing a mass of necrotic neutrophils, bacteria and tissue debris
3. The entire necrotic mass is surrounded by a fibrous connective tissue capsule/cyst wall
4. The cyst wall is formed by proliferating capillaries, inflammatory cells, and gliosis

Gliosis

Granulation tissue

Liquefactive necrosis



	COAGULATIVE	LIQUIFACTIVE	CASSEOUS	FIBRINOID	FAT
INTRO					
CAUSES					
GROSS					
MICRO					

Types of Necrosis (CCCCFF)

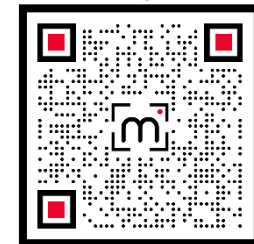
- 5 types→

- Coagulative necrosis (most common)
- Colliquative / Liquefactive necrosis
- Caseous
- Fat necrosis
- Fibrinoid necrosis

Caseous necrosis (cheese like)

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- **Introduction**
- **Causes**
- **Gross**
- **Microscopy**

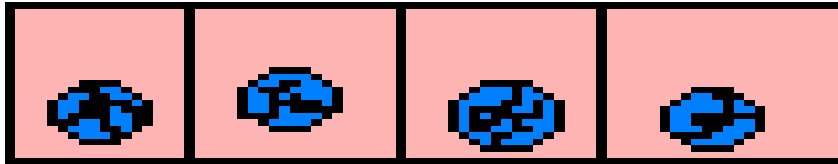
INTRODUCTION

- Dead tissue is converted into a **homogenous, granular mass resembling cottage cheese.**
- **Their architectural details as well as cytoplasmic and nuclear details are lost**
- **Accumulation of amorphous (no structure) debris within an area of necrosis**

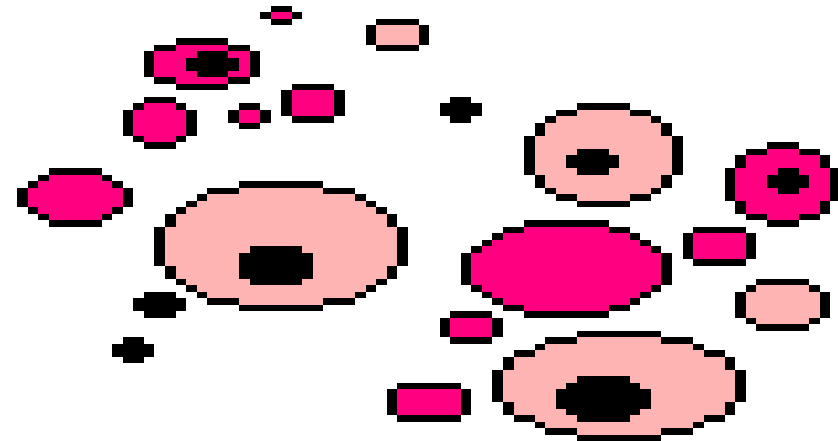


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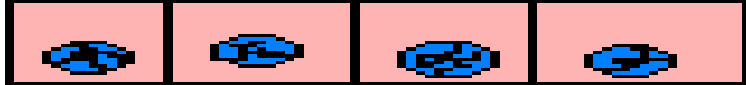
Alive



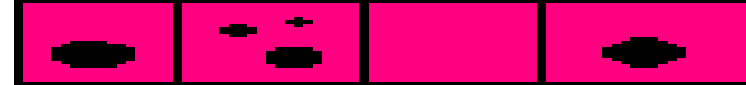
Caseous Necrosis



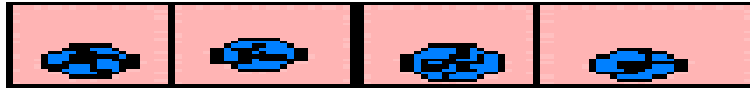
Alive



**Coagulation
Necrosis**



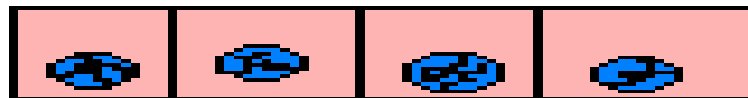
Alive



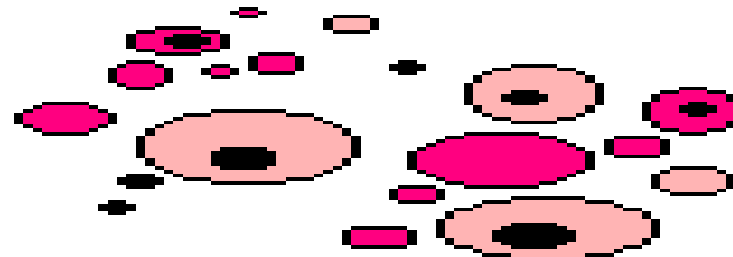
**Liquefaction
Necrosis**



Alive



**Caseous
Necrosis**



Cause:

- Associated with lesions of **Mycobacterium tuberculosis, syphilis and fungi (Histoplasma, Coccidioidomycosis)**

Gross appearance

- Foci of caseous necrosis resemble **dry cheese and are soft, granular and yellowish.**
- This appearance is partly attributed to the histotoxic effects of **lipopolysaccharides present in the capsule of the tubercle bacilli, Mycobacterium tuberculosis**



Figure 2-13 Caseous necrosis. Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white and cheesy debris.

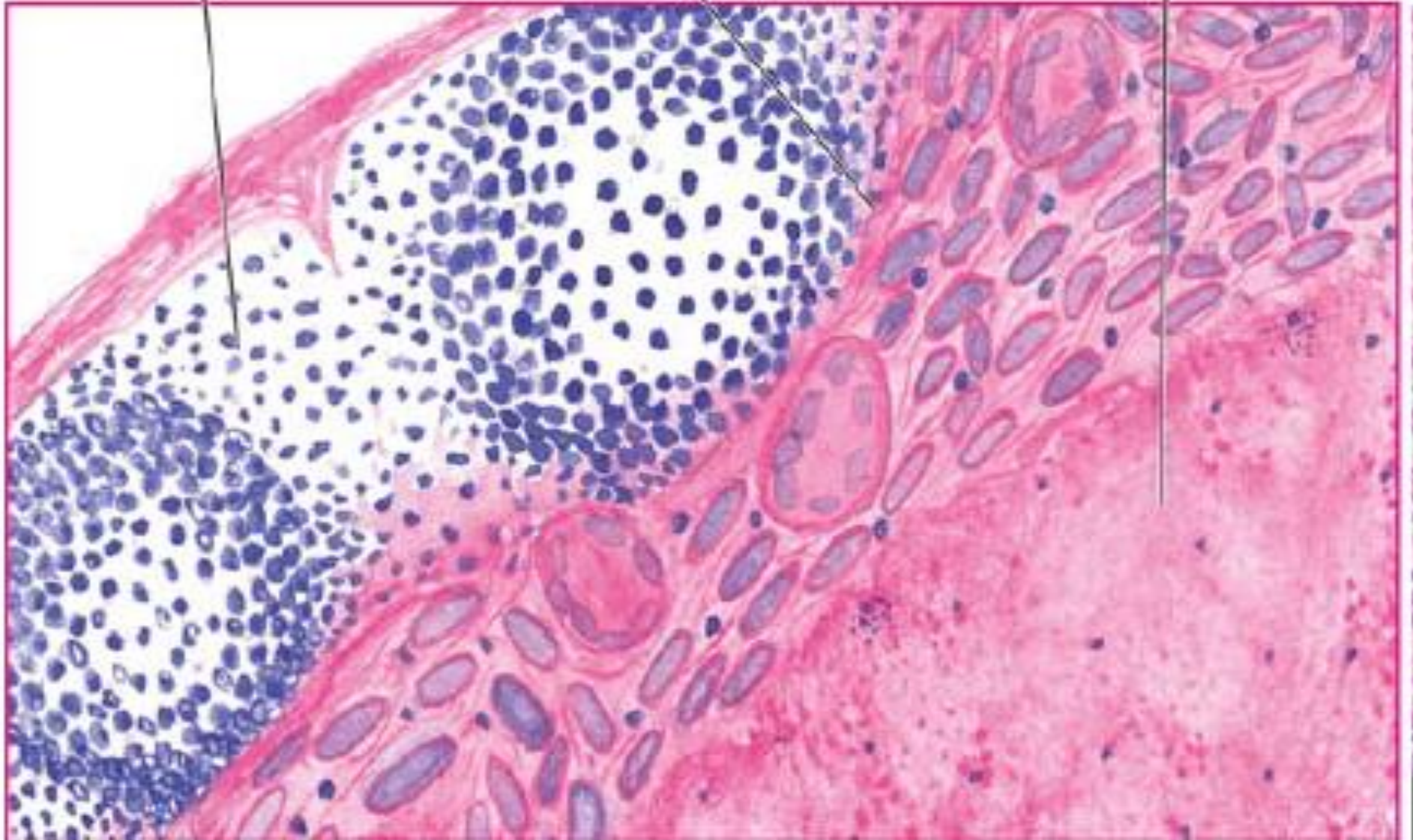
Microscopically

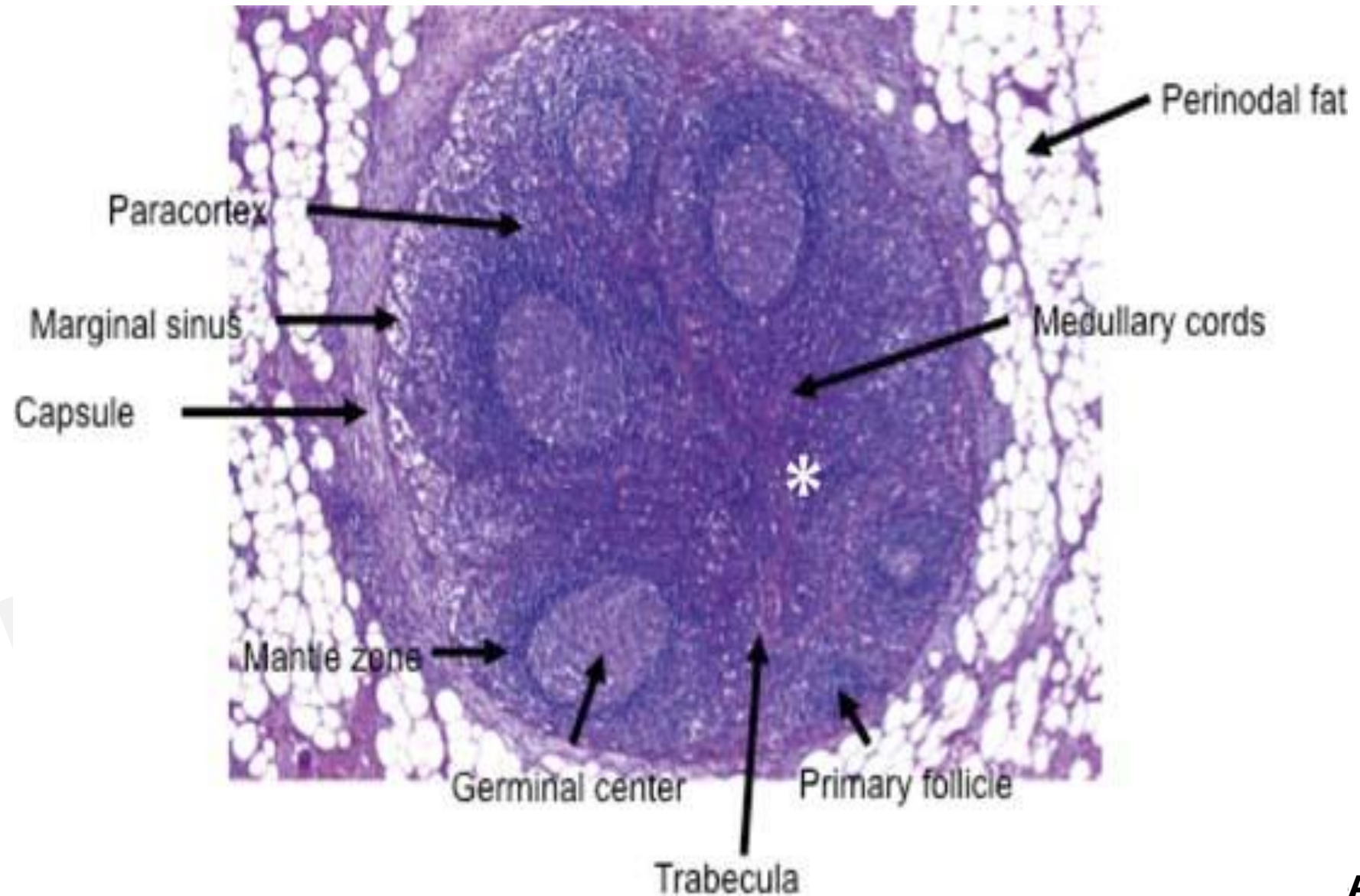
- **Centre** of the necrosed focus contain **structureless, eosinophilic material having scattered granular debris of disintegrated nuclei**
- The **surrounding tissue** shows characteristic **granulomatous inflammatory reaction** consisting of epithelioid cells (modified macrophages having slipper-shaped vesicular nuclei), interspersed giant cells of Langhans' and foreign body type and peripheral mantle of lymphocytes

Viable lymphoid tissue

Granulomatous inflammation

Caseous necrosis





	COAGULATIVE	LIQUIFACTIVE	CASSEOUS	FIBRINOID	FAT
INTRO					
CAUSES					
GROSS					
MICRO					

Types of Necrosis (CCCCFF)

- 5 types→

- Coagulative necrosis (most common)
- Colliquative / Liquefactive necrosis
- Caseous
- Fat necrosis
- Fibrinoid necrosis

Fat necrosis

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- **Introduction**
- **Causes**
- **Gross**
- **Microscopy**

INTRODUCTION

- Fat necrosis is a special form of cell death occurring at mainly **fat-rich anatomic locations** in the body.
- **Death of adipose tissue in a living animal**

Causes

- Pancreatic (acute pancreatitis)
- Traumatic (breast)

Grossly

- Fat necrosis appears as **yellowish-white and firm deposits.**
- Formation of calcium soaps imparts the necrosed foci firmer and **chalky white appearance**

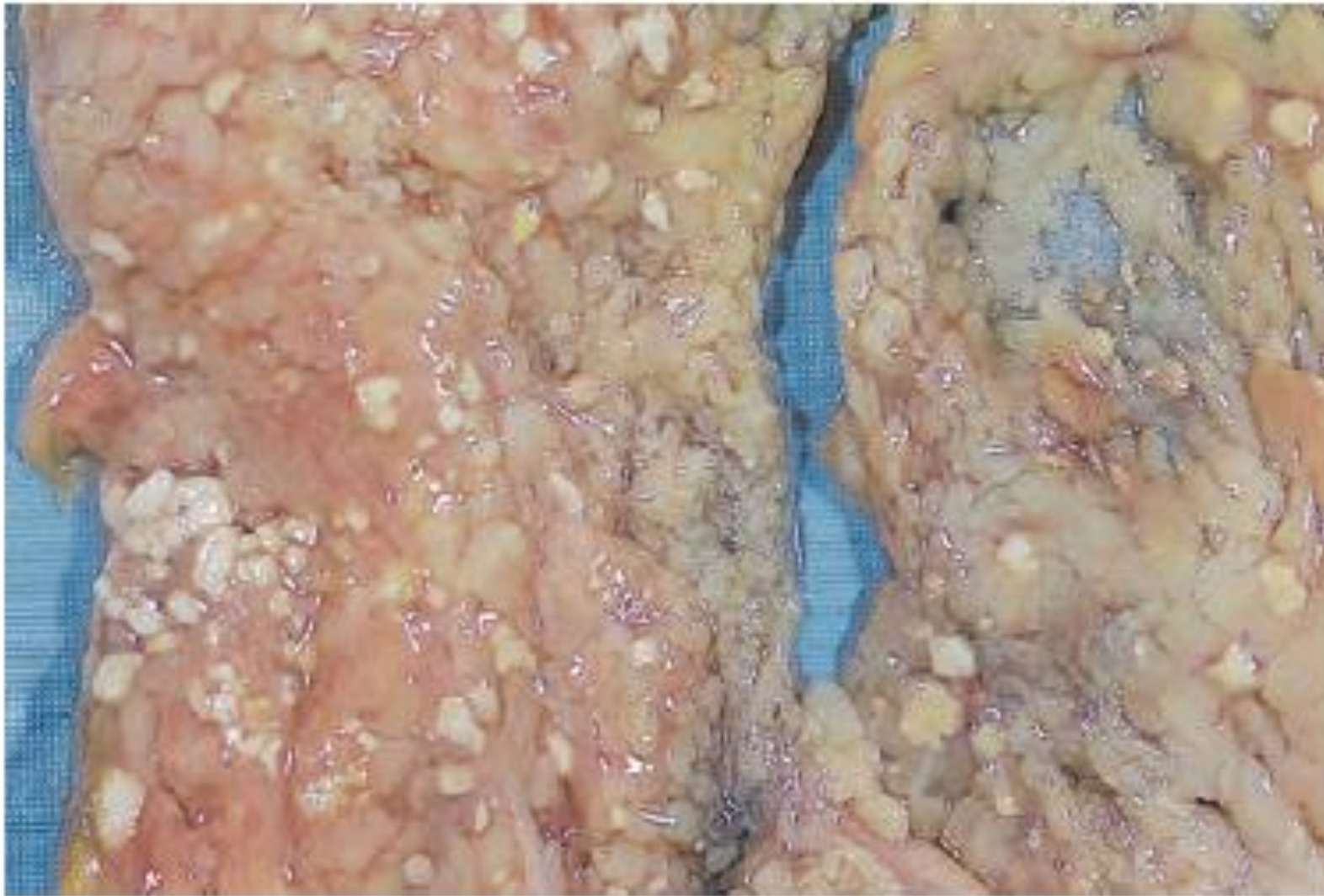


Figure 2-14 Fat necrosis. The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.



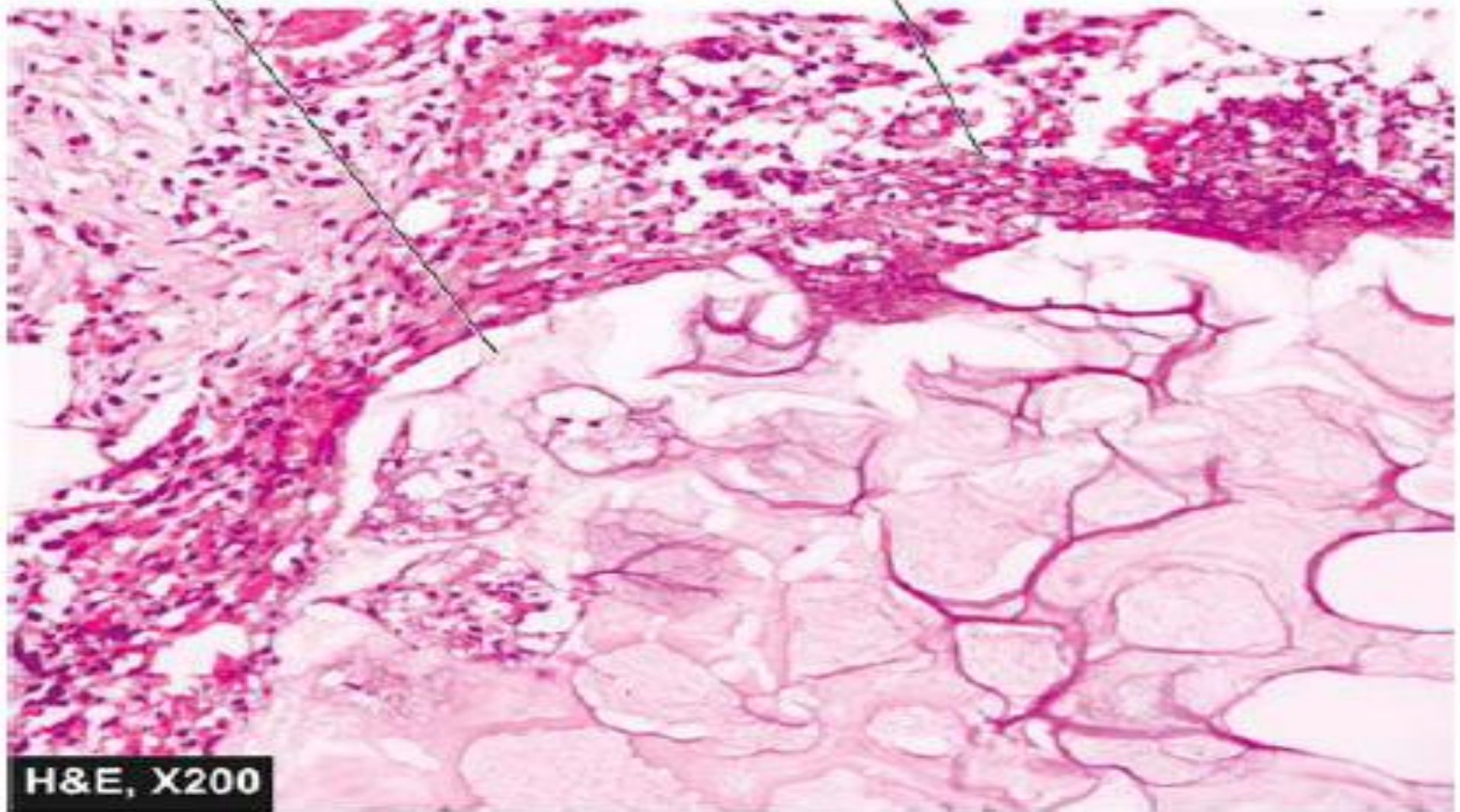
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Microscopically

- The necrosed fat cells have **cloudy appearance**
- They are surrounded by an **inflammatory reaction.**
- Formation of calcium soaps is identified in the tissue sections as **amorphous, granular and basophilic material**

Cloudy appearance

Mixed inflammatory cells



H&E, X200

Types of Necrosis (CCCCFF)

- 5 types→

- Coagulative necrosis (most common)
- Colliquative / Liquefactive necrosis
- Caseous
- Fat necrosis
- Fibrinoid necrosis

Fibrinoid Necrosis

- Fibrinoid necrosis is characterized by **deposition of fibrin-like material** which has the staining properties of fibrin
- The fibrin like material is deposited in **wall of blood vessels**

Causes

- **Immunologic injury of vessel wall** (e.g. in immune complex vasculitis, autoimmune diseases, Arthus reaction etc), arterioles in hypertension, peptic ulcer etc.

Microscopically

- Fibrinoid necrosis is identified by **brightly eosinophilic, hyaline-like deposition in the vessel wall.**
- Necrotic focus is surrounded by **nuclear debris of neutrophils (leucocytoclasia)**
- **Local haemorrhage** may occur due to rupture of the blood vessel.

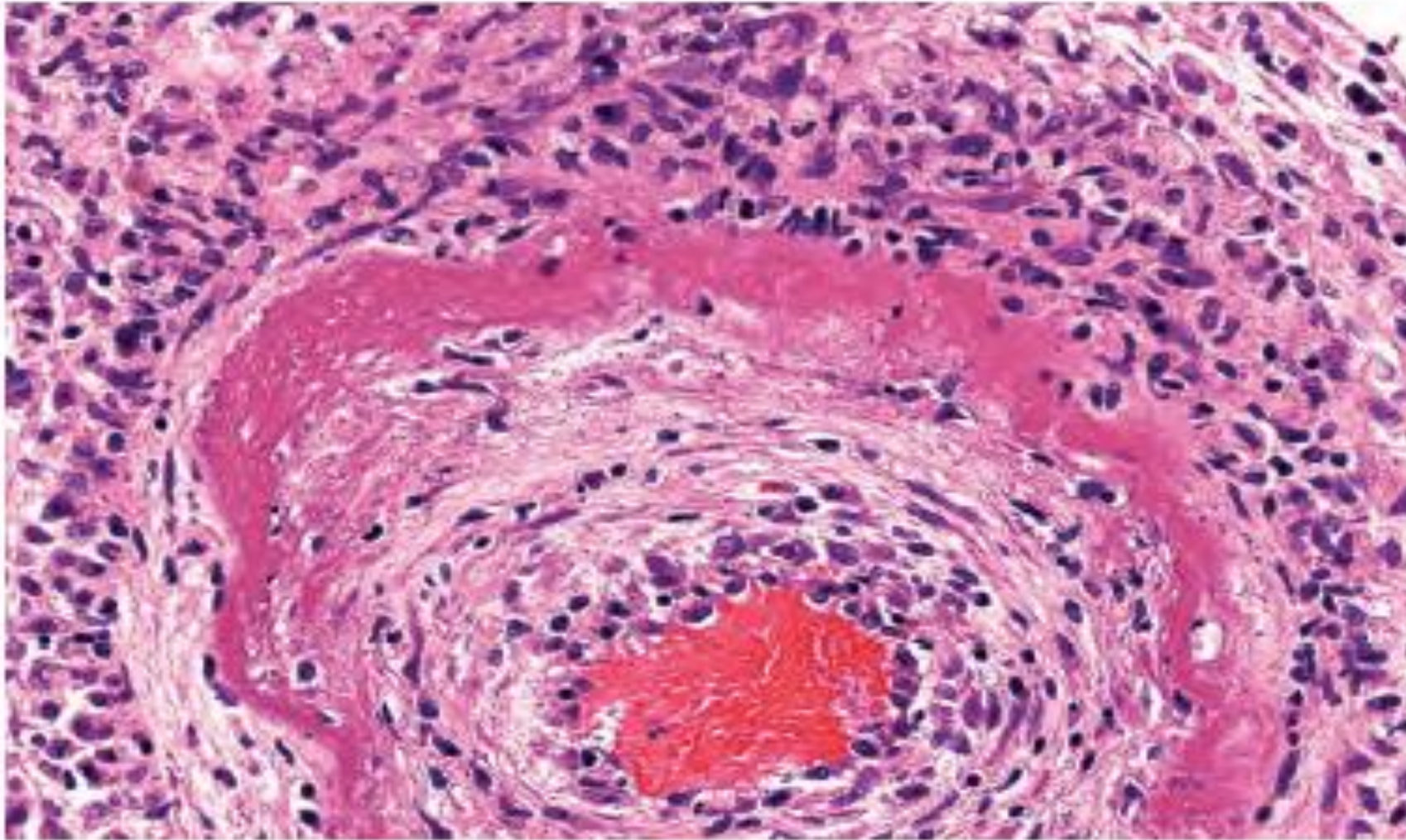


Figure 2-15 Fibrinoid necrosis in an artery. The wall of the artery shows a circumferential bright pink area of necrosis with inflammation (neutrophils with dark nuclei).

	COAGULATIVE	LIQUIFACTIVE	CASSEOUS	FIBRINOID	FAT
INTRO					
CAUSES					
GROSS					
MICRO					

REVISION

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Cell Adaptation & Injury*



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Apoptosis & Necrosis*



*Scan or Click to watch
Inflammation*



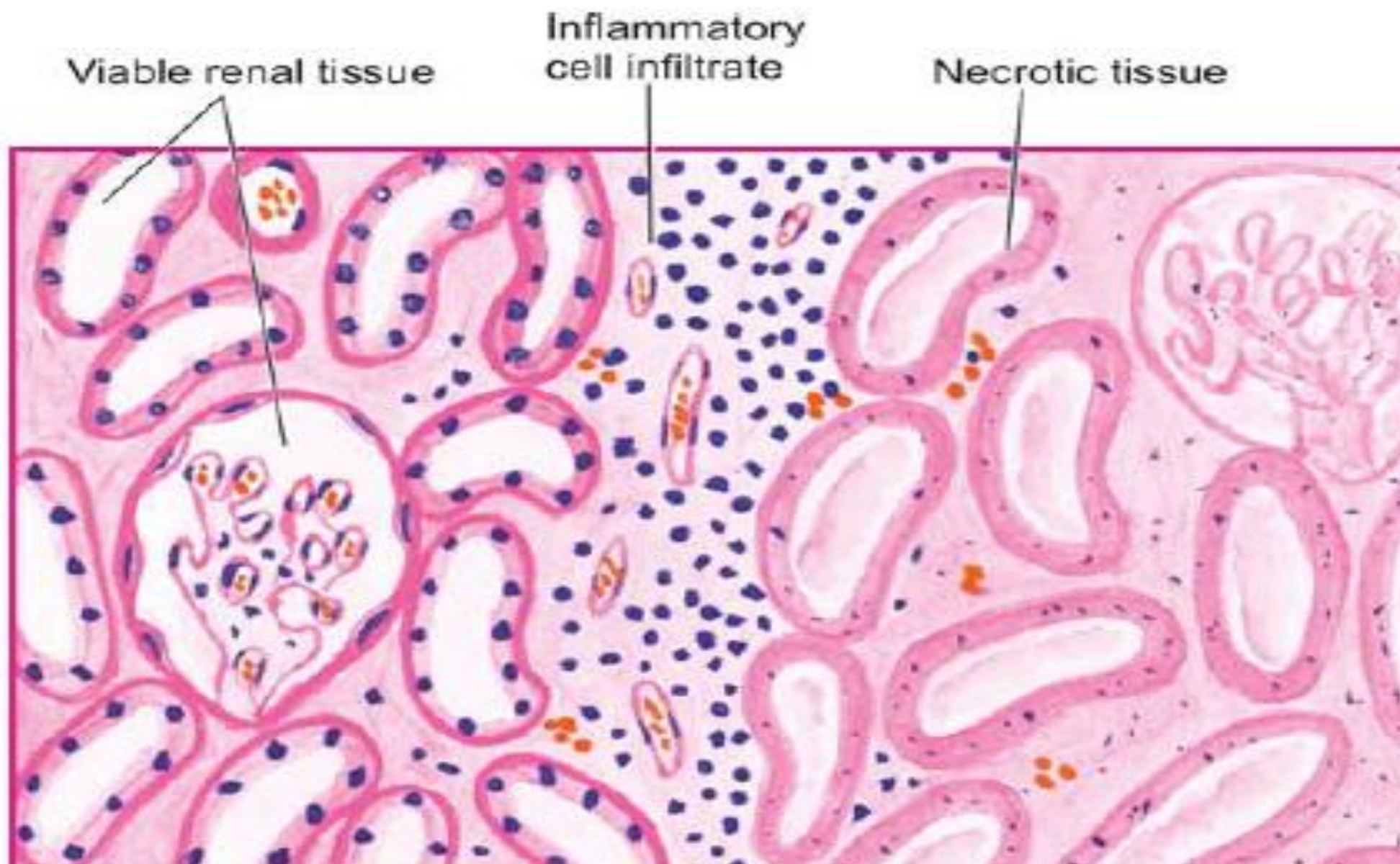
*Scan or Click to watch
Haemodynamic Disorder*



Types of Necrosis (CCCCFF)

- 5 types→

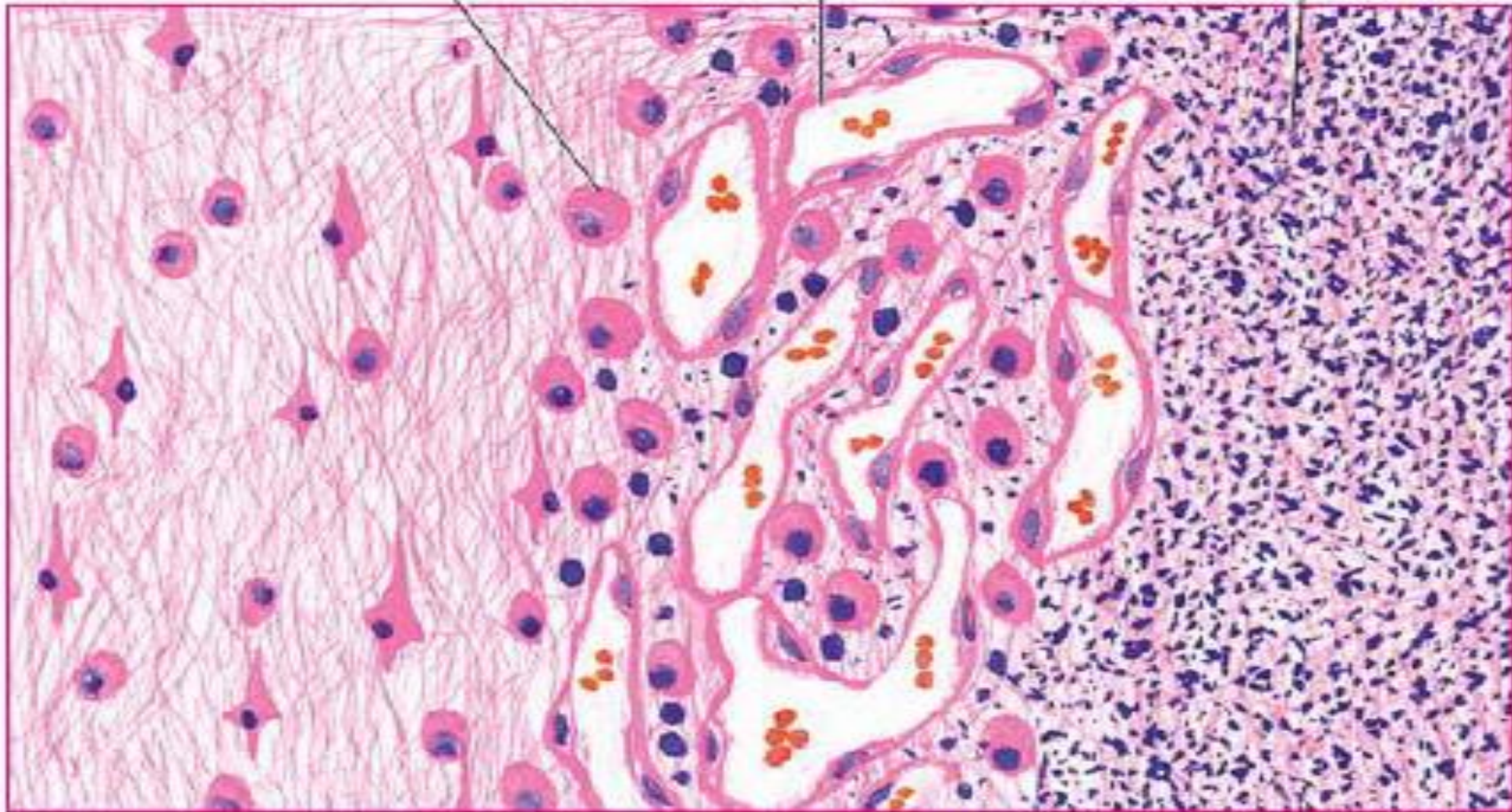
- Coagulative necrosis (most common)
- Colliquative / Liquefactive necrosis
- Caseous
- Fat necrosis
- Fibrinoid necrosis

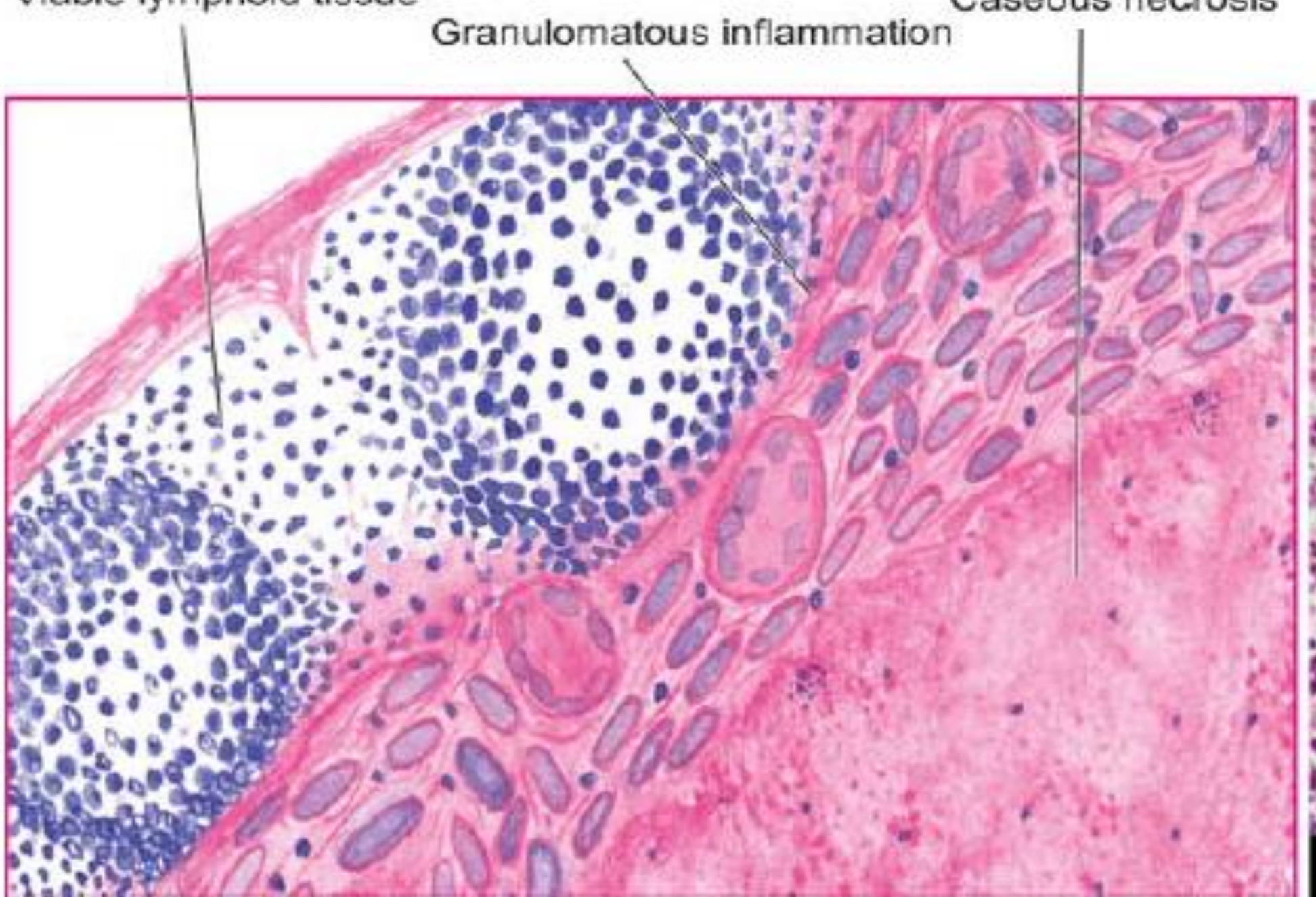


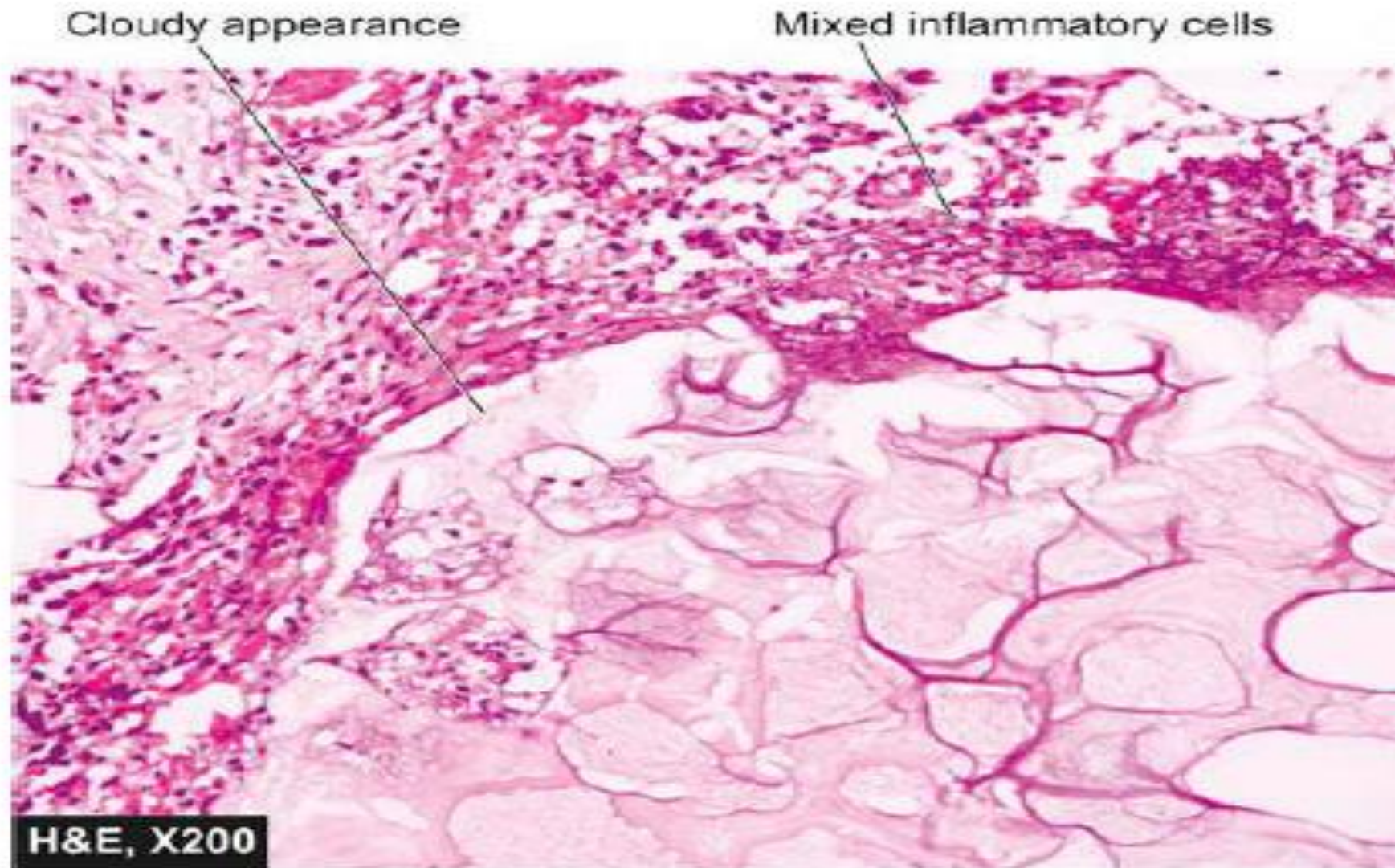
Gliosis

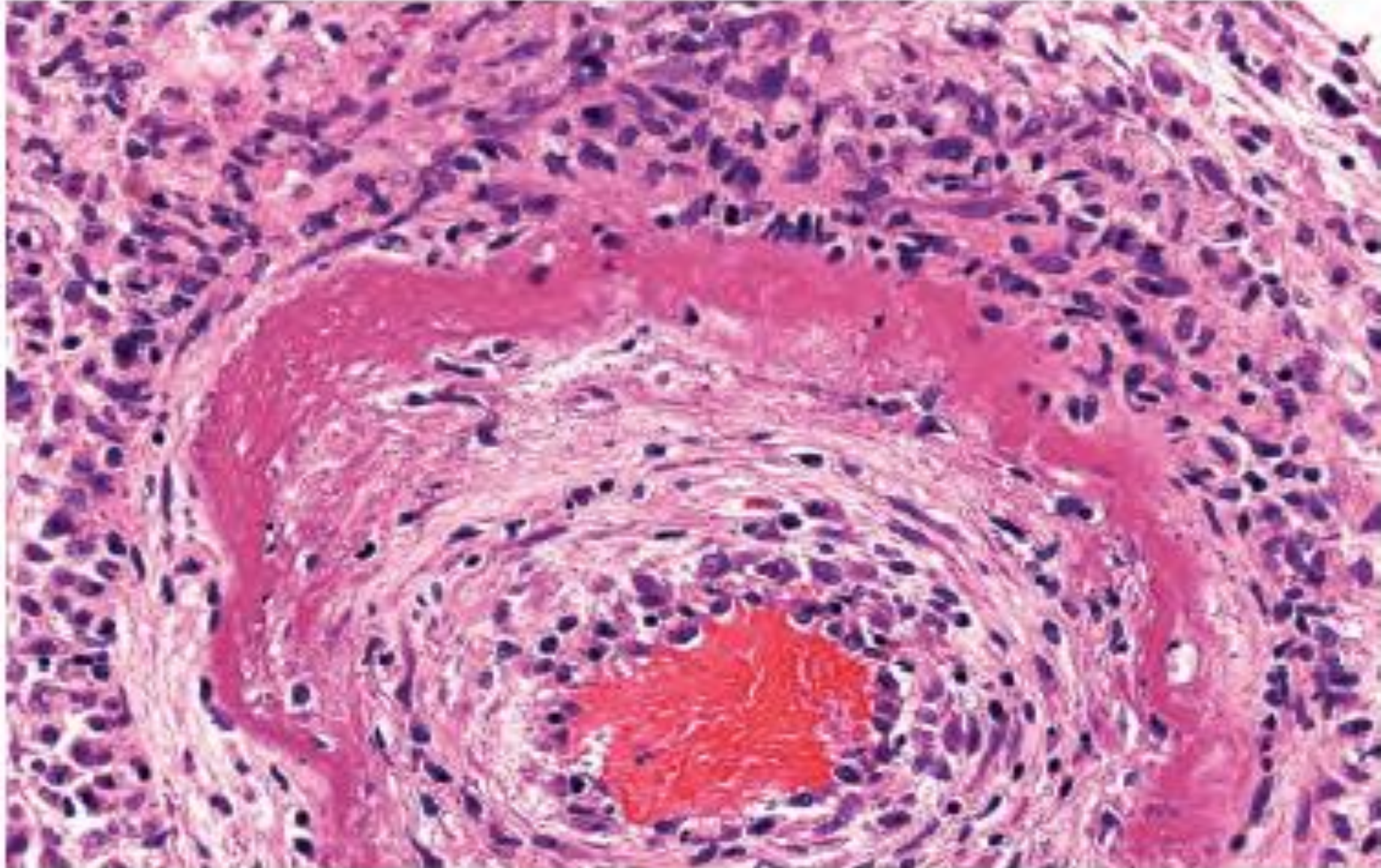
Granulation tissue

Liquefactive necrosis









	COAGULATIVE	LIQUIDFACTIVE	CASSEOUS	FIBRINOID	FAT
INTRO					
CAUSES					
GROSS					
MICRO					

POLLS 6

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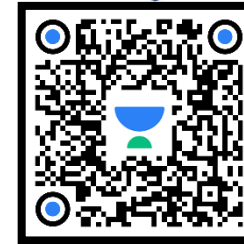
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*Scan or Click to watch
Inflammation*



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Haemodynamic Disorder*



Necrosis with cell bodies retained as ghost cells is

- a) Coagulative necrosis
- b) Liquefactive
- c) Caseous
- d) None

Necrosis with cell bodies retained as ghost cells is

- a) Coagulative necrosis
- b) Liquefactive
- c) Caseous
- d) None

All the following organs likely undergo coagulative necrosis except

- a) Spleen
- b) Heart
- c) Kidney
- d) Brain

All the following organs likely undergo coagulative necrosis except

- a) Spleen
- b) Heart
- c) Kidney
- d) Brain

Liquefactive necrosis is seen in -

- a) Heart
- b) Brain
- c) Lungs
- d) Spleen

Liquefactive necrosis is seen in -

- a) Heart
- **b) Brain**
- c) Lungs
- d) Spleen

Spread of infection causes -

- a) Fibrinoid necrosis**
- b) Fat necrosis**
- c) Liquifactive necrosis**
- d) Coagulative necrosis**

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C

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MI is a type of -

- a) Coagulative necrosis
- b) Liquefactive necrosis
- c) Caseous necrosis
- d) Fat necrosis

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A

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Coagulative necrosis is seen in A/E -

- a) M.I.
- b) T.B.
- c) Thermal
- d) Zenker's degeneration

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Type of necrosis in pancreatitis-

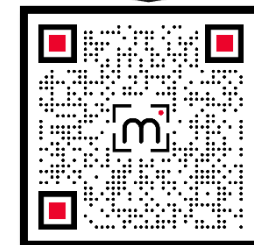
- a) Fibrinoid
- b) Coagulative
- c) Fat
- d) Caseous

Dr. -

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Trauma to breast causes which type of necrosis -

- a) Coagulative necrosis
- b) Liquefactive necrosis
- c) Caseous necrosis
- d) Fat necrosis

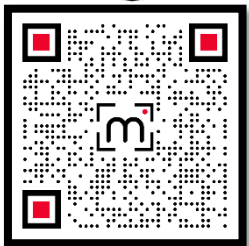
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GANGRENE

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Like us



Headings

- Definition
- Types—>
 - a) Introduction
 - b) Gross
 - c) Microscopy

DEFINITION

- Gangrene is **necrosis of tissue associated with superadded putrefaction**

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- **GANGRENE = Necrosis + Putrefaction**

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Headings

- Definition
- Types—>
 - a) Introduction
 - b) Gross
 - c) Microscopy

TYPES

2 main types of gangrene—

1. Dry

2. Wet

3. A variant of wet gangrene called **gas gangrene.**

1. **“Dry” gangrene** – **no bacterial superinfection**; tissue appears dry

2. **“Wet” gangrene** – **bacterial superinfection** has occurred; tissue looks wet and liquefactive

- In all types of gangrene, necrosis undergoes liquefaction by the action of putrefactive bacteria.

Headings

- Definition
- Types—>
 - a) Introduction
 - b) Gross
 - c) Microscopy

Dry Gangrene

- Begins in the **distal part of a limb (toes ,feet)**
- Due to **ischaemia** (blockage of **artery**).
- spreads **slowly** upwards until where the blood supply is adequate to keep the tissue viable.
- A **line of separation** is formed at this point between the gangrenous part and the viable part

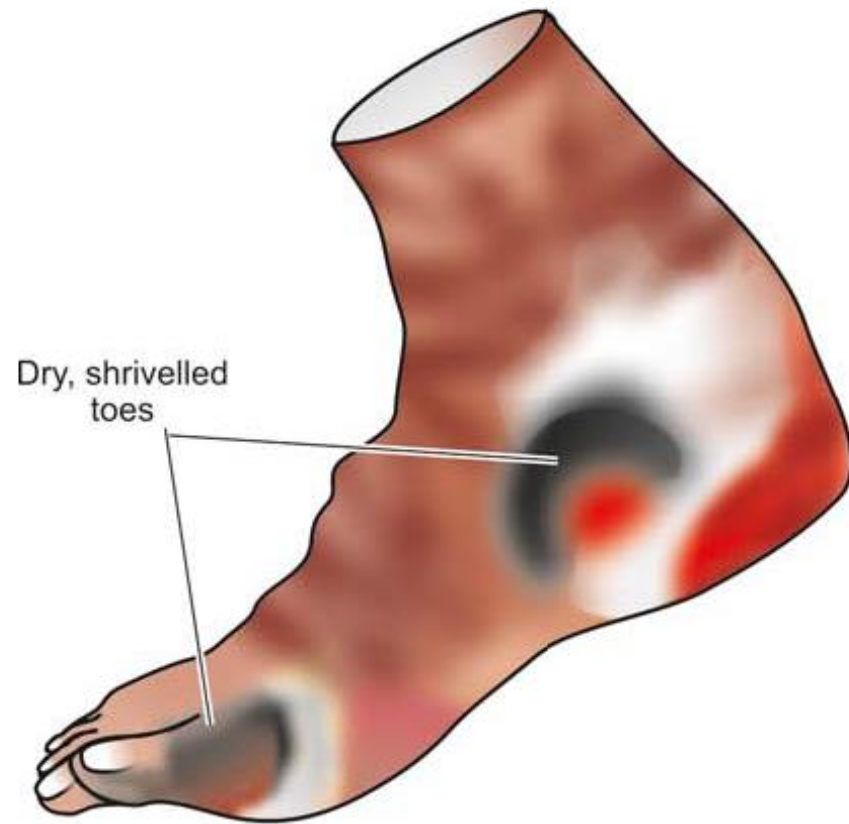


Figure 2.29 Dry gangrene of the foot. The gangrenous area is dry, shrunken and dark and is separated from the viable tissue by clear line of separation.

- It is a type of **coagulative necrosis**
- The extent of vascular occlusion is frequently global in the lower limbs, which impedes or prevents the migration of leukocytes in to the area of coagulative necrosis
- It is called gangrenous necrosis because **the dead tissue is not digested and removed but remains mummified.**

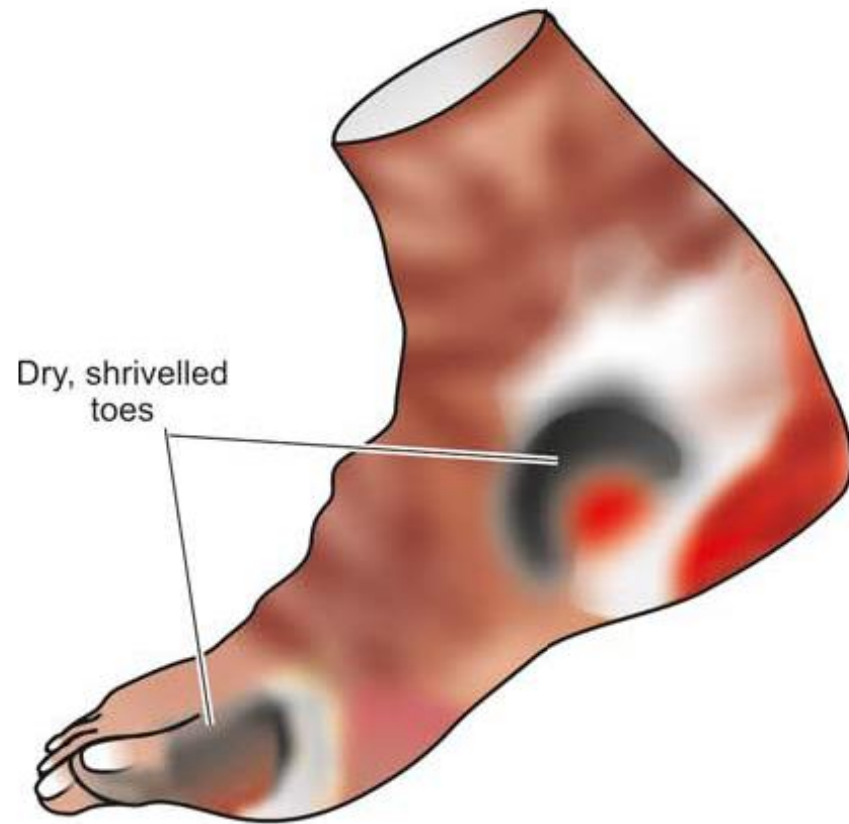


Figure 2.29 Dry gangrene of the foot. The gangrenous area is dry, shrunken and dark and is separated from the viable tissue by clear line of separation.

Headings

- Definition
- Types—>
 - a) Introduction
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 - c) Microscopy

Grossly

- Affected part is **dry, shrunken and dark black, resembling the foot of a mummy.**
- It is **black** due to liberation of haemoglobin from haemolysed red blood cells which is acted upon by hydrogen disulfide (H_2S) produced by bacteria resulting in formation of black iron sulfide.
- **Line of separation**

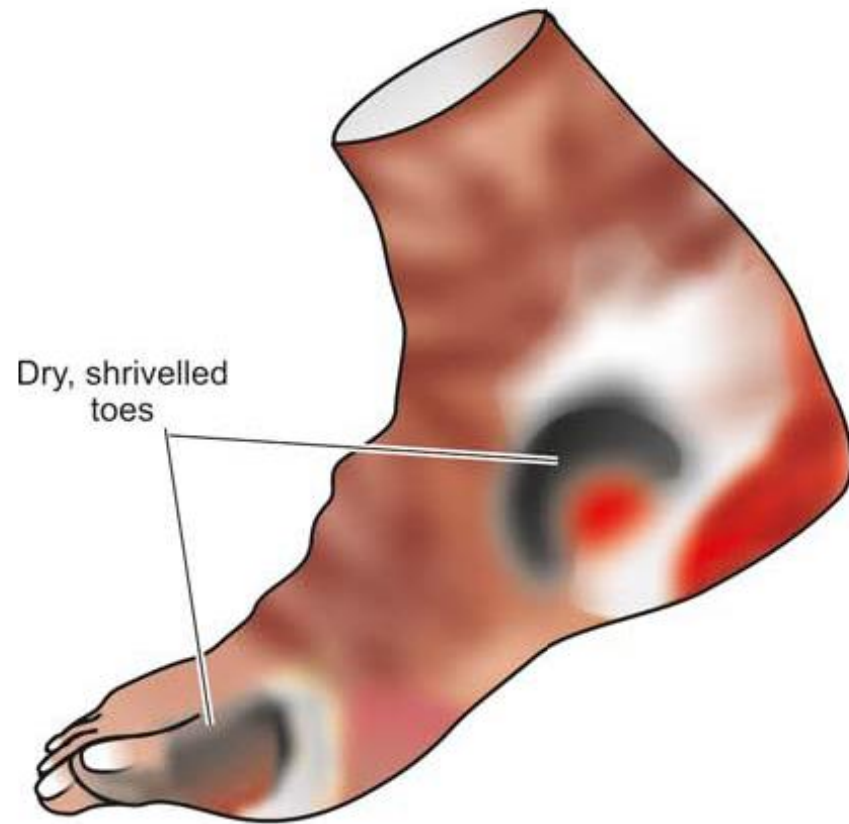


Figure 2.29 Dry gangrene of the foot. The gangrenous area is dry, shrunken and dark and is separated from the viable tissue by clear line of separation.



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Histologically

- There is coagulative necrosis with smudging of the tissue.
- Line of separation consists of inflammatory granulation tissue

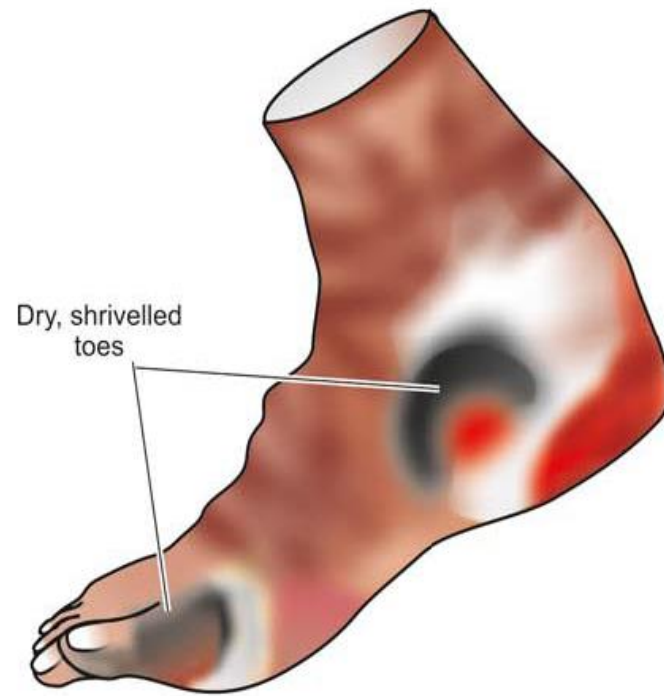


Figure 2.29 Dry gangrene of the foot. The gangrenous area is dry, shrunken and dark and is separated from the viable tissue by clear line of separation.

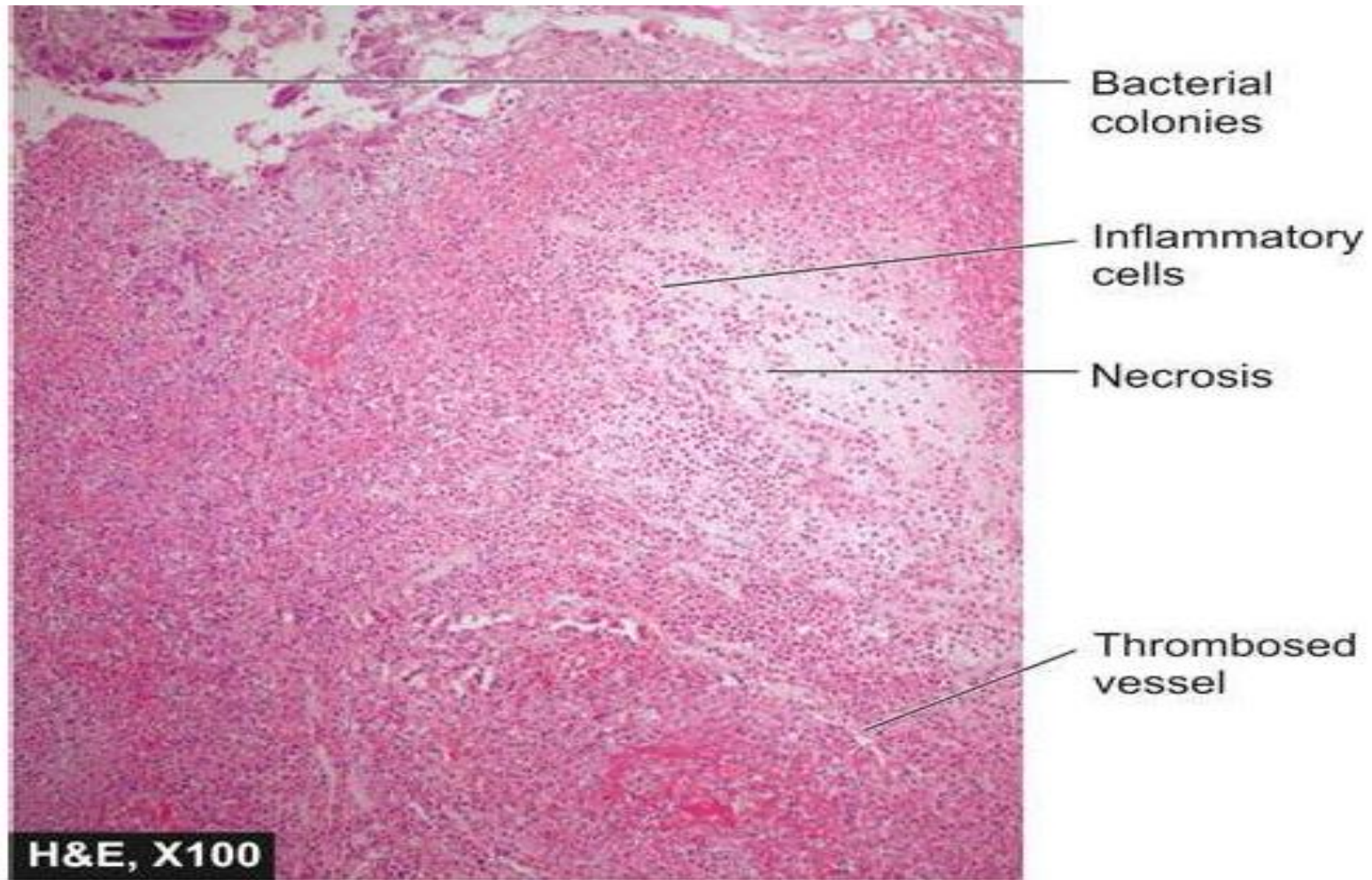


Figure 2.30 Dry gangrene of the foot. Microscopy shows coagulative necrosis of the skin, muscle and other soft tissue, and thrombosed vessels.

Headings

- Definition
- Types—>
 - a) Introduction
 - b) Gross
 - c) Microscopy

Wet Gangrene

- When overlying skin of dry gangrenous tissue is devitalized, **bacterial infection is superimposed**
- The coagulative necrosis is modified by **liquifactive necrosis.**

- Occurs in naturally **moist tissues and organs** such as the bowel, lung, mouth, cervix, vulva
- Develops due to blockage of **both venous as well as arterial blood flow**
- More **rapid.**
- **NO clear-cut line of demarcation**

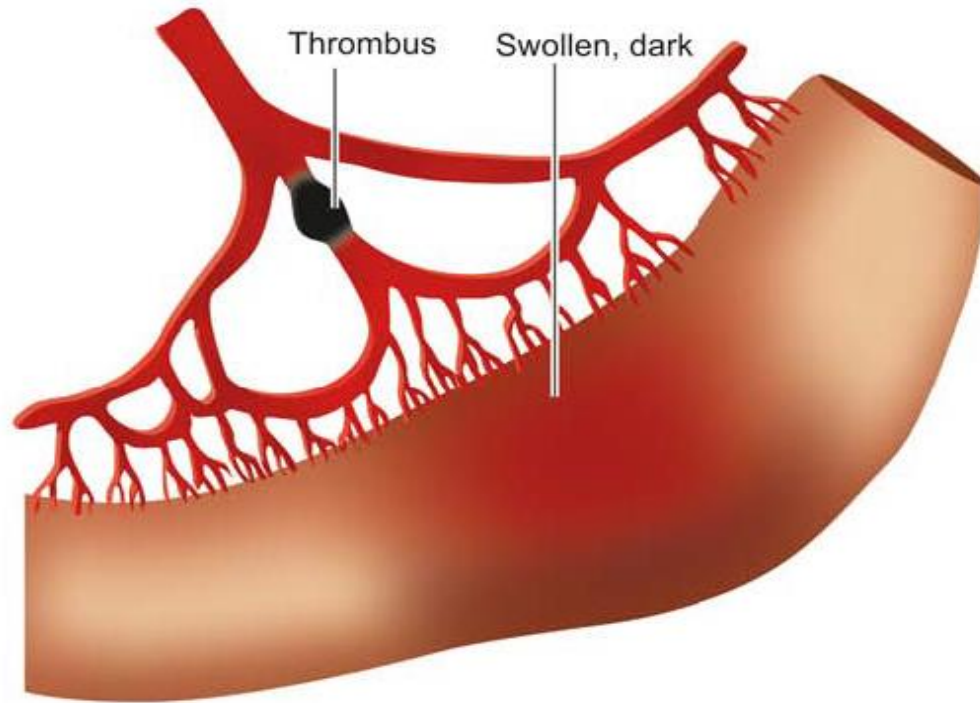


Figure 2.31 Wet gangrene of the small bowel. The affected part is soft, swollen and dark. Line of demarcation between gangrenous segment and the viable bowel is not clear-cut.



- The classic example is **gangrene of the bowel, commonly due to strangulated hernia.**
- **Diabetic foot** which is due to high glucose content favours growth of bacteria.

Headings

- Definition
- Types—>
 - a) Introduction
 - b) Gross
 - c) Microscopy

Grossly

the affected part is **soft, swollen, putrid, rotten and dark.**

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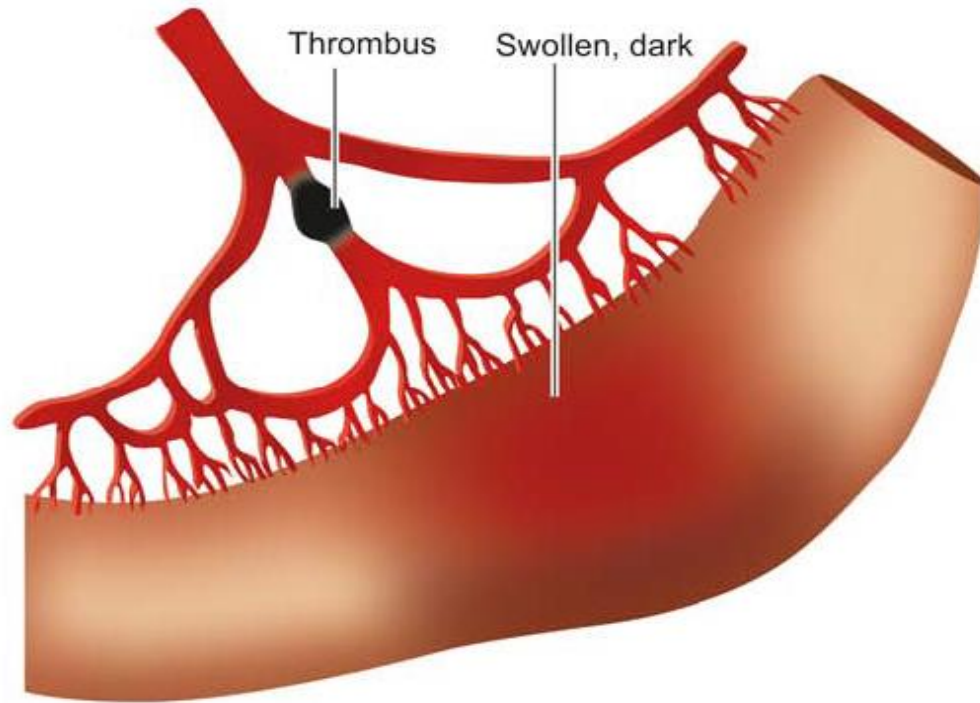


Figure 2.31 Wet gangrene of the small bowel. The affected part is soft, swollen and dark. Line of demarcation between gangrenous segment and the viable bowel is not clear-cut.



Histologically

- There is coagulative necrosis
- Mucosa is ulcerated and sloughed.
- Intense acute inflammatory exudates and
- Thrombosed vessel

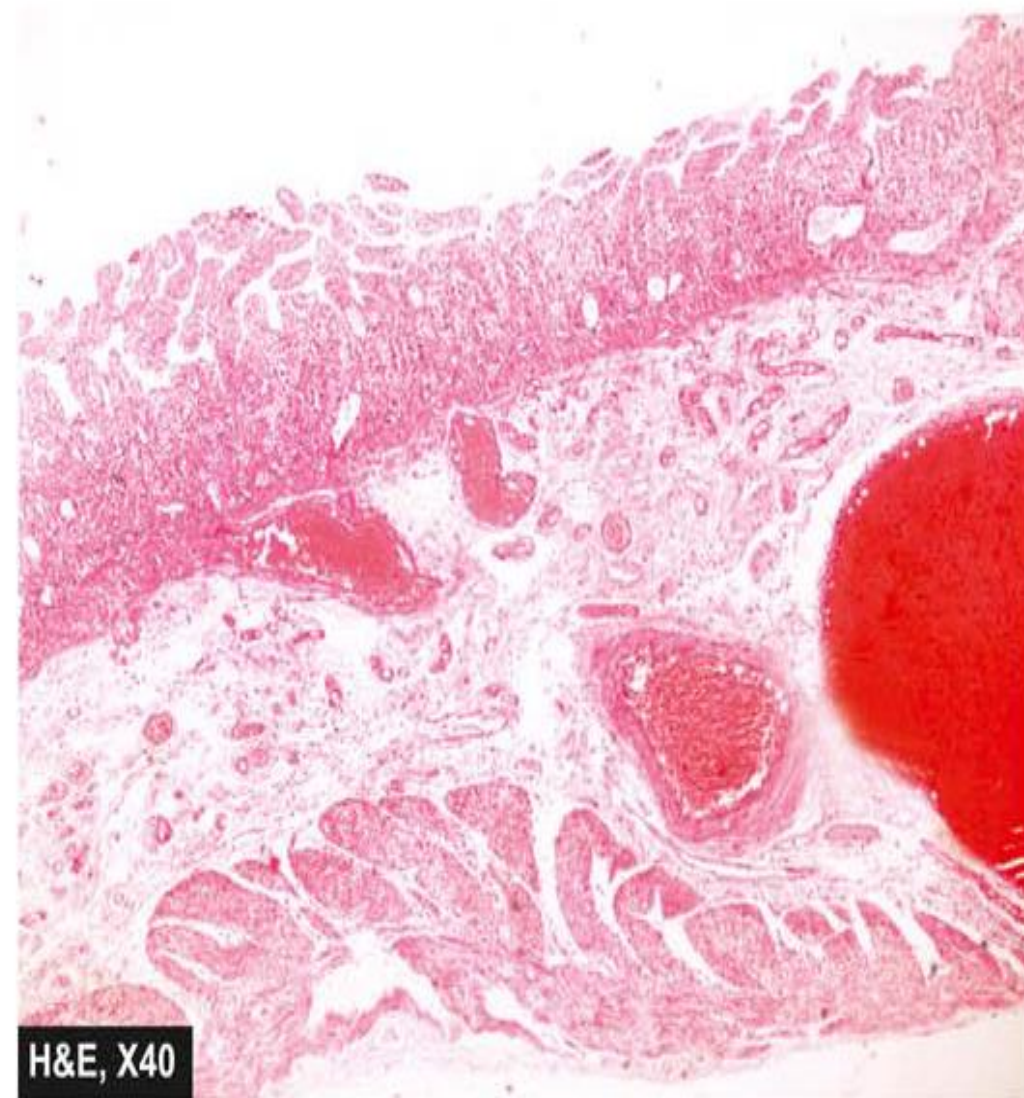
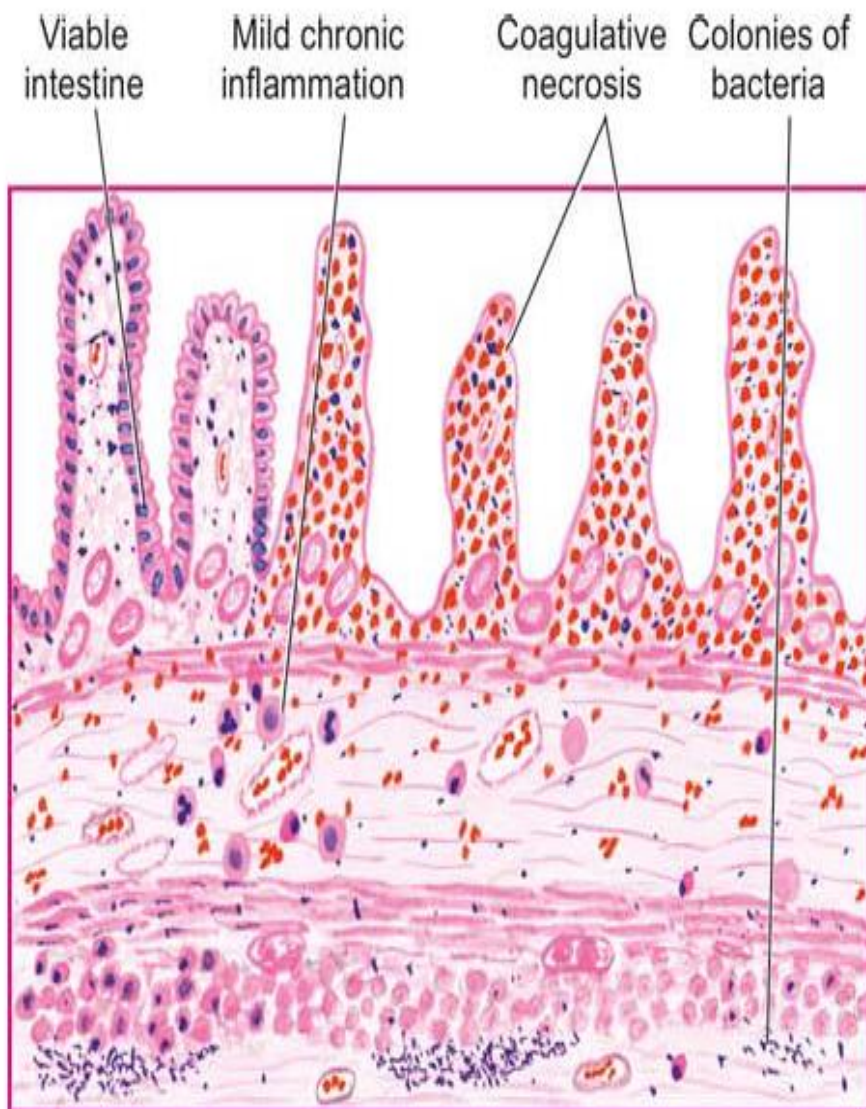


Figure 2.32 Wet gangrene of the small bowel. Microscopy shows coagulative necrosis of the affected bowel wall and thrombosed vessels while the junction with normal intestine is indistinct and shows an inflammatory infiltrate.

FEATURE	DRY GANGRENE	WET GANGRENE
1. <i>Site</i>	Commonly limbs	More common in bowel
2. <i>Mechanisms</i>	Arterial occlusion	Blockage of both venous drainage and arterial obstruction
3. <i>Macroscopy</i>	Organ dry, shrunken and black	Part moist, soft, swollen, rotten and dark
4. <i>Putrefaction</i>	Limited due to very little blood supply	Marked due to stuffing of organ with blood
5. <i>Line of demarcation</i>	Present at the junction between healthy and gangrenous part	No clear line of demarcation
6. <i>Bacteria</i>	Bacteria fail to survive	Numerous present
7. <i>Prognosis</i>	Generally better due to little septicaemia	Generally poor due to profound toxemia

REMEMBER

- **Dry gangrene** -> Variant of Coagulative necrosis
- **Wet gangrene** -> Liquifactive necrosis is superimposed on coagulative necrosis

Headings

- Definition
- Types—>
 - a) Introduction
 - b) Gross
 - c) Microscopy

GAS GANGRENE

- Special form of wet gangrene caused by **gas-forming clostridia (gram-positive anaerobic bacteria)**
- It enters through open contaminated wounds or complication of operation on colon which normally contains clostridia.

Headings

- Definition
- Types—>
 - a) Introduction
 - b) Gross
 - c) Microscopy

Grossly

- **Swollen, oedematous, painful and crepitant** due to accumulation of gas bubbles of carbon dioxide within the tissues formed by fermentation of sugars by bacterial toxins



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Microscopically

- Coagulative necrosis with liquefaction.
- Large number of gram-positive bacilli can be identified.
- leucocytic infiltration, oedema
- Capillary and venous thrombi are common.

POLLS 7

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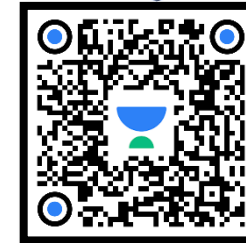
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Inflammation*



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Liquefactive action on necrotic tissue results in -

- a) Gangrene
- b) Embolism
- c) Infarct
- d) Caseation

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Infected gangrene of skin and subcutaneous tissues is?

- a) Dry gangrene
- b) Wet gangrene
- c) Erysipelas
- d) None of the above

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Diabetic foot is associated with following type of gangrene?

- a) Dry gangrene
- b) Wet gangrene
- c) Gas gangrene
- d) Fournier's gangrene

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B

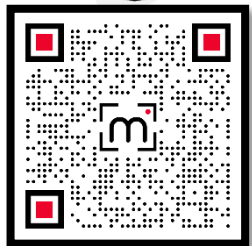
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Pathological calcification

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CALCIUM

Insoluble inorganic calcium salts are a normal constituent of **bones and teeth.**



CALCIUM

- The great majority of the calcium in the body is stored in bone and teeth
- The bulk of remaining calcium is bound to protein or forms small ionic complexes.
- It is estimated that **1% or less of the calcium** in the body is present in ionic form, the active form of the element.

CALCIUM

- Furthermore, the calcium concentration **outside of cells** is approximately 10,000 fold higher than inside cells.
- Within cells, calcium is 10,000 fold higher in the **endoplasmic reticulum and mitochondria** than in the cytosol.

CALCIUM HOMEOSTASIS

- **Vitamin D (1,25-dihydroxycholecalciferol)**
- **Parathormone**
- **Calcitonin**

Vitamin D (1,25-dihydroxycholecalciferol):

Stimulus

- Low extracellular calcium
- Parathormone stimulates formation of 1,25-dihydroxycloecalciferol by the kidney

Main Action – lead to increased extracellular calcium

- increase the absorption of calcium and phosphorus from the intestine.

Parathormone

Stimulus

- Low extracellular calcium
- Elevated extracellular phosphorus

Main actions – lead to increased extracellular calcium

- Stimulates formation of vitamin D by the kidney
- Increased mobilization of calcium from bone
- Increasing absorption of calcium from the intestine
- Promotes resorption of calcium from the kidney
- Promotes excretion of phosphorus in the urine

Calcitonin

Stimulus

- Elevated extracellular calcium

Action – lowers extracellular calcium

- Inhibits the parathormone-induced release of calcium from bone
- Promotes the urinary excretion of phosphorus

PATHOLOGICAL CALCIFICATION

- **Deposition of calcium salts in tissues other than osteoid or enamel is called pathologic or heterotopic calcification**
- **It is abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium and mineral salts in cells and tissues that are not normally mineralized.**

TYPES

2 forms:

1. Dystrophic

2. Metastatic

Dystrophic calcification:

- Calcification of **dead and dying tissues.**
- The level of calcium in blood is usually normal. (There is **no hypercalcemia**).
- Calcification occurs in two phases-initiation and propagation

- within the cells or extra-cellularly
1. Extracellular initiation occurs in **small vesicles derived from degenerating cells**
 2. Initiation of intra-cellular calcification occurs in the **mitochondria** of dead or dying cells.

Membrane of dead and degenerated cell damaged,



```
graph TD; A[Membrane of dead and degenerated cell damaged,] --> B[Phospholipid is released]; B --> C[Phosphatases within the phospholipid generate phosphate ions]; C --> D[calcium binds to phosphate ions]; D --> E[forming calcium phosphate];
```

Phospholipid is released

Phosphatases within the phospholipid generate phosphate ions

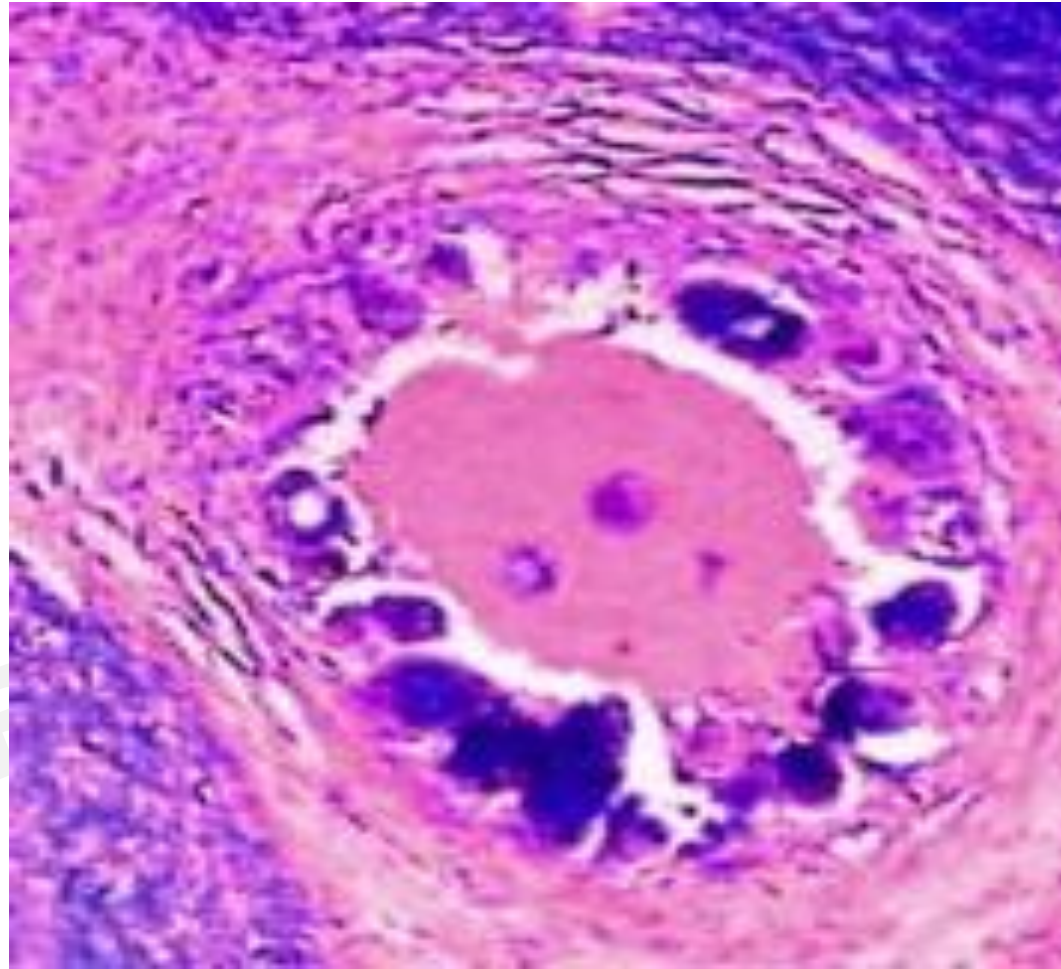
calcium binds to phosphate ions

forming calcium phosphate

Sites of calcification:

Dead tissues

- caseation eg. Tuberculosis
- Dead parasites like trichinosis, Onchocercosis.
- fat necrosis
- infarcts
- thrombi
- haematoma



Sites of calcification:

Degenerative tissues

- – atherosclerosis- monckeberg sclerosis
- – damaged heart valves
- – infected lymph nodes
- – degenerating tumours

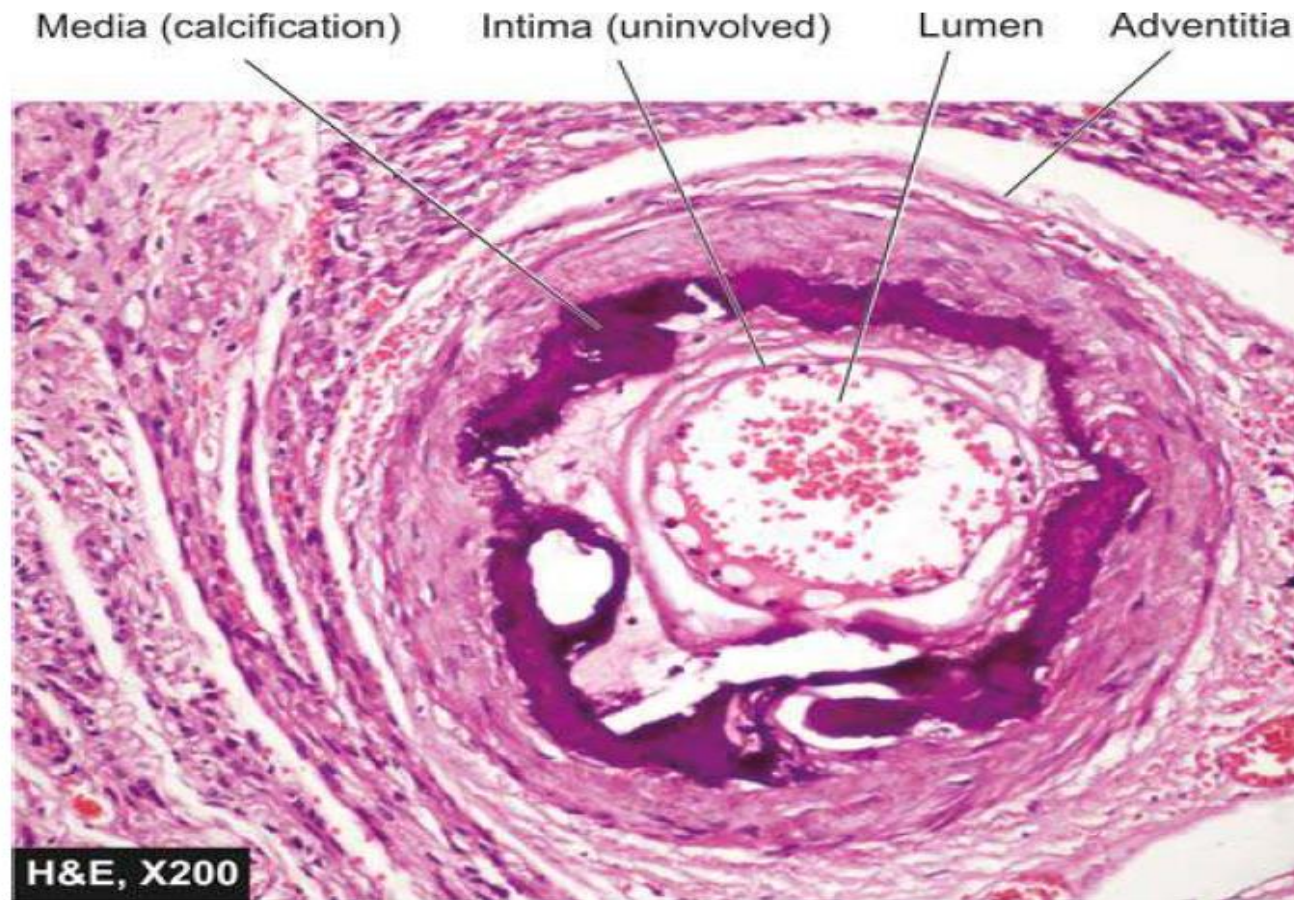
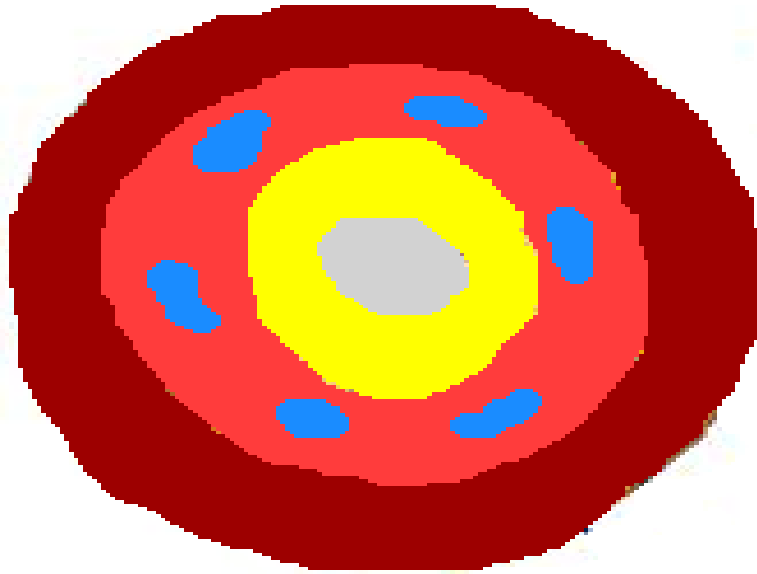
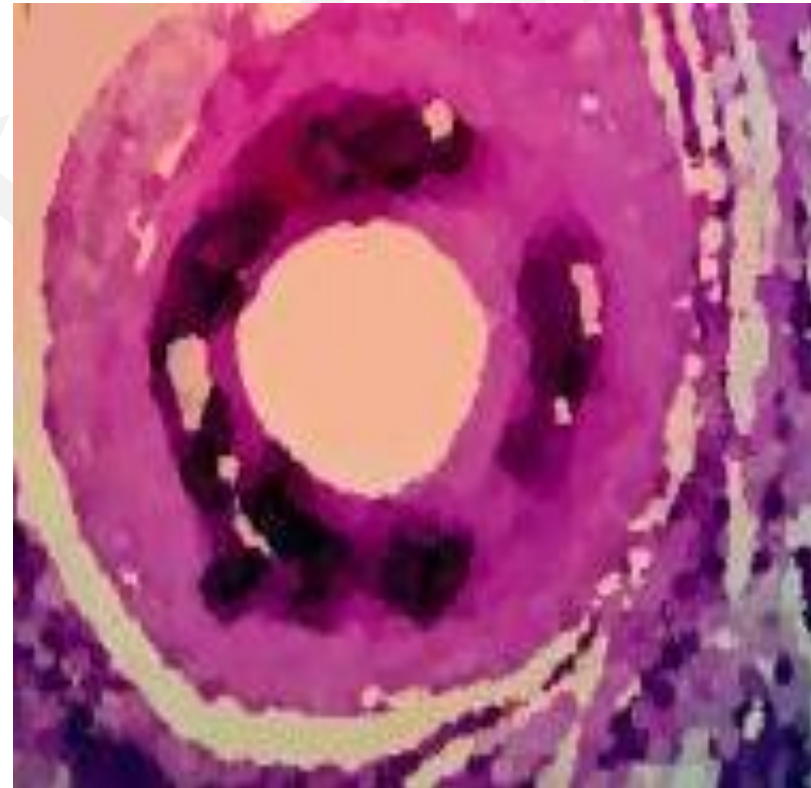


Figure 2.34 Dystrophic calcification in degenerated tunica media of muscular artery of uterine myometrium in Mönckeberg's arteriosclerosis.



**Monckeberg's Sclerosis -
Calcification of Tunica
Media.**



Dystrophic calcification in dead tissues

- In caseous necrosis of tuberculosis (**most common which may be in lymph nodes**^(NEET))
- Chronic abscess in liquifactive necrosis
- Fungal granuloma
- Infarct
- Thrombi
- Haematomas
- Dead parasites-Cystecercosis/Toxoplasma
Hydatid/Schistosoma
- In fat necrosis of breast & other tissues

Dystrophic calcification in degenerated tissues

- **Atheromatous plaque**^(AI 13)
- Monkeberg's sclerosis
- **Psommama bodies**^(DNB 08)
- Dens old scars
- Senile degenrated changes such as in costal cartilage, tracheal, bronchial rings, Pineal gland in brain.
- **Heart valves damaged by rheumatic fever**^(NEET).

TYPES

2 forms:

1. Dystrophic

2. Metastatic

Metastatic calcification

It is deposition of calcium salts in many **tissues which may be normal.**

It is associated with disorders of calcium metabolism and there is **hypercalcemia.**

It may occur widely throughout the body, hence the term “metastatic.”

Those organs that 'lose' acid

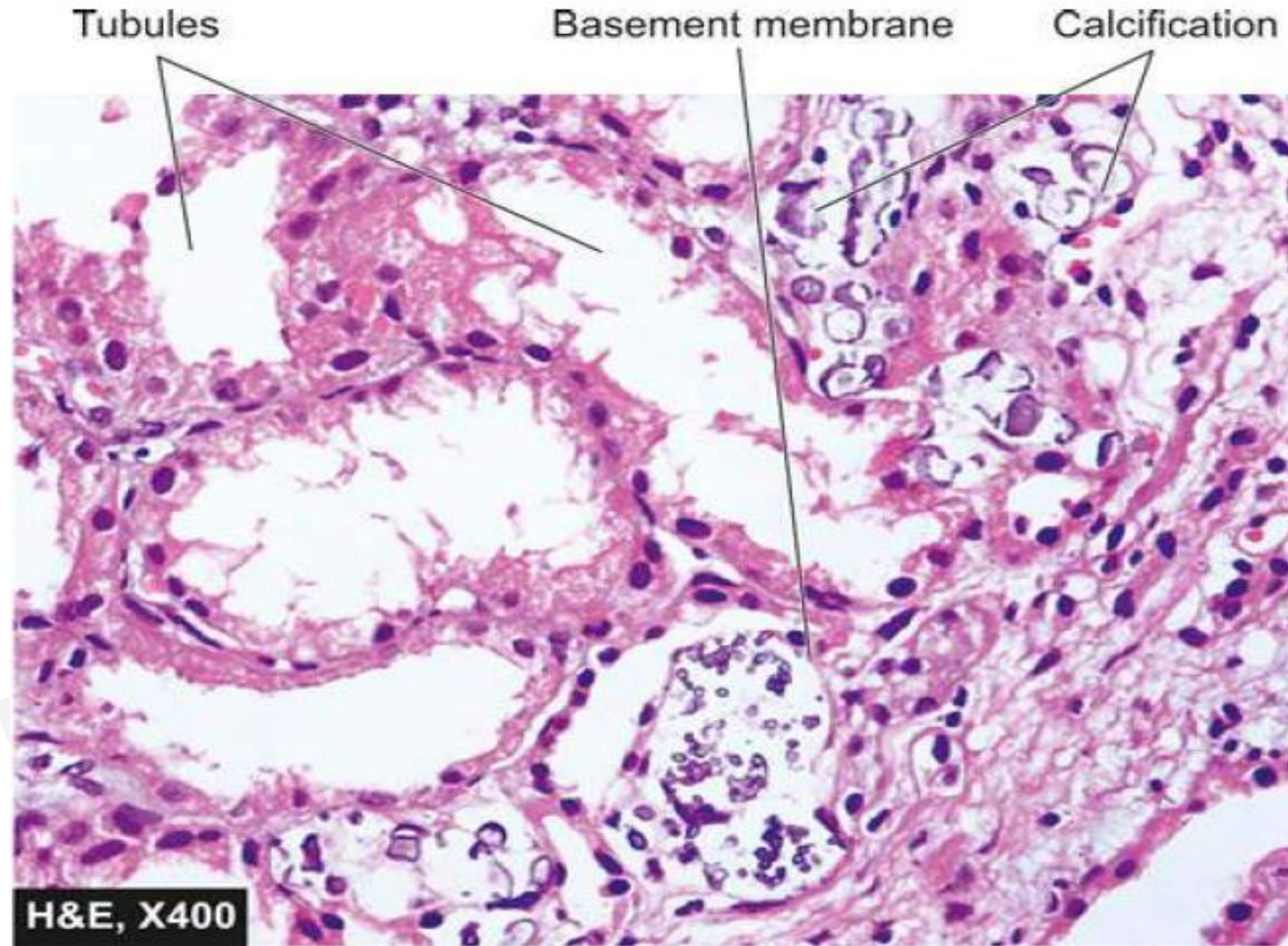
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graph TD; A[Those organs that 'lose' acid] --> B[Have an underlying alkaline compartment.]; B --> C[An alkaline internal component is susceptible to calcification.];
```

Have an underlying alkaline compartment.

An alkaline internal component is susceptible to calcification.

Sites of calcification:

- Basement membrane & tubular lamina of kidney^(NEET, AIIMS 05)
- Pulmonary veins
- Alveolar wall of lung (most common site)^(NEET, AIIMS 05)
- Cornea & Conjunctiva
- Interstitial tissue of gastric mucosa^(AIIMS 05)
- Synovium of the joint
- Systemic arteries
- Tendons.



Causes:

- 1. Hyperparathyroidism-** A. Primary, due to neoplasm
B. Secondary-nutritional or renal failure (uremia)
- 2. Hypervitaminosis-D** (Vit.D Toxicosis). Increased absorption of Ca from intestine.
- 3. Neoplasms:** Lymphosarcoma and apocrine adenocarcinoma secrete parathyroid hormone-like peptides and cause hypercalcemia.

TYPES

2 forms:

1. Dystrophic

2. Metastatic

- **Gross and microscopic appearance is similar to dystrophic and metastatic calcification.**

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Gross

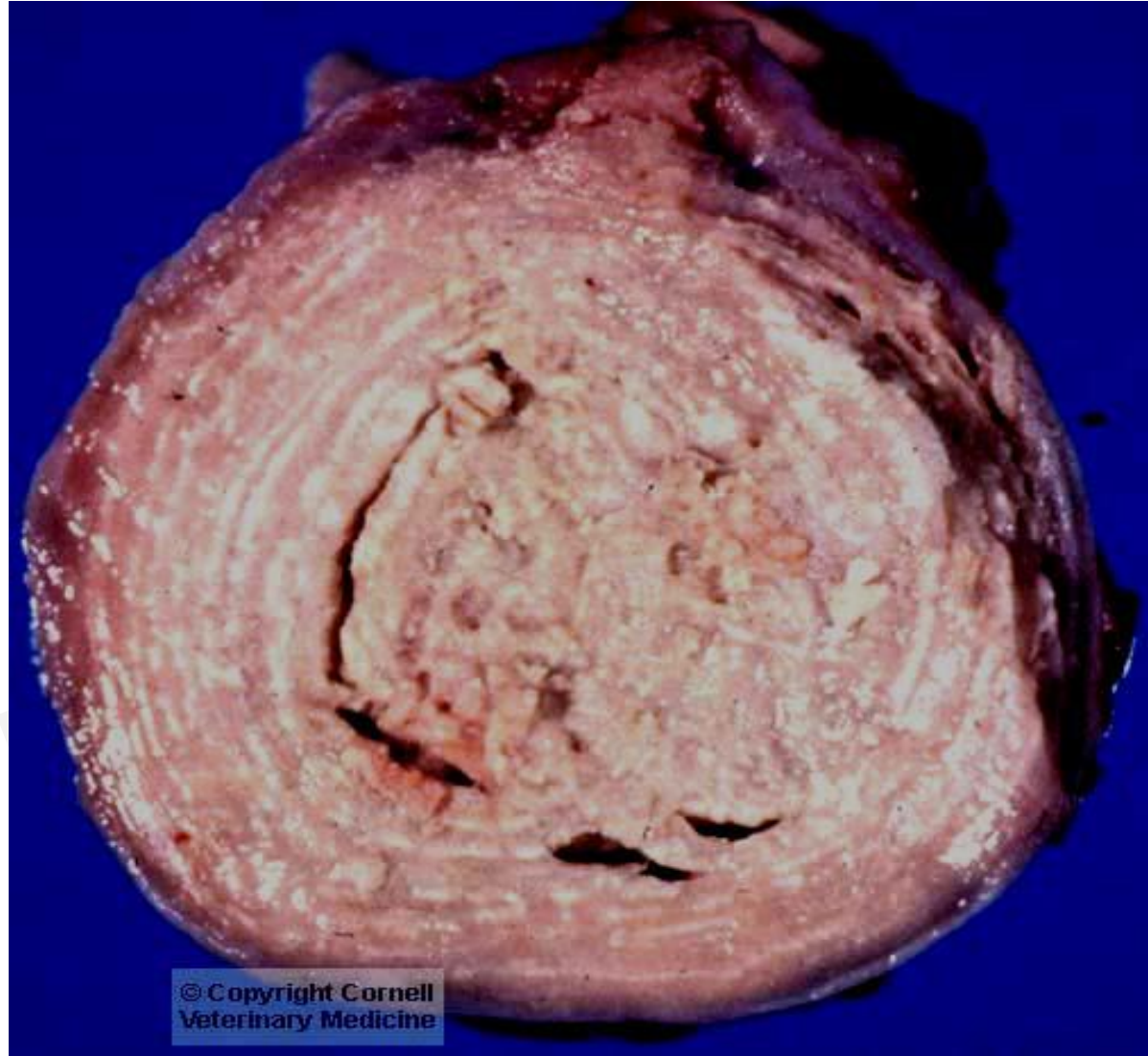
- Calcification appears as **pale chalky white** areas in the tissues.
- Even if not visible, calcification can sometimes be detected by the **coarse gritty feel** of the tissues when scraped or incised with a knife or scalpel blade.



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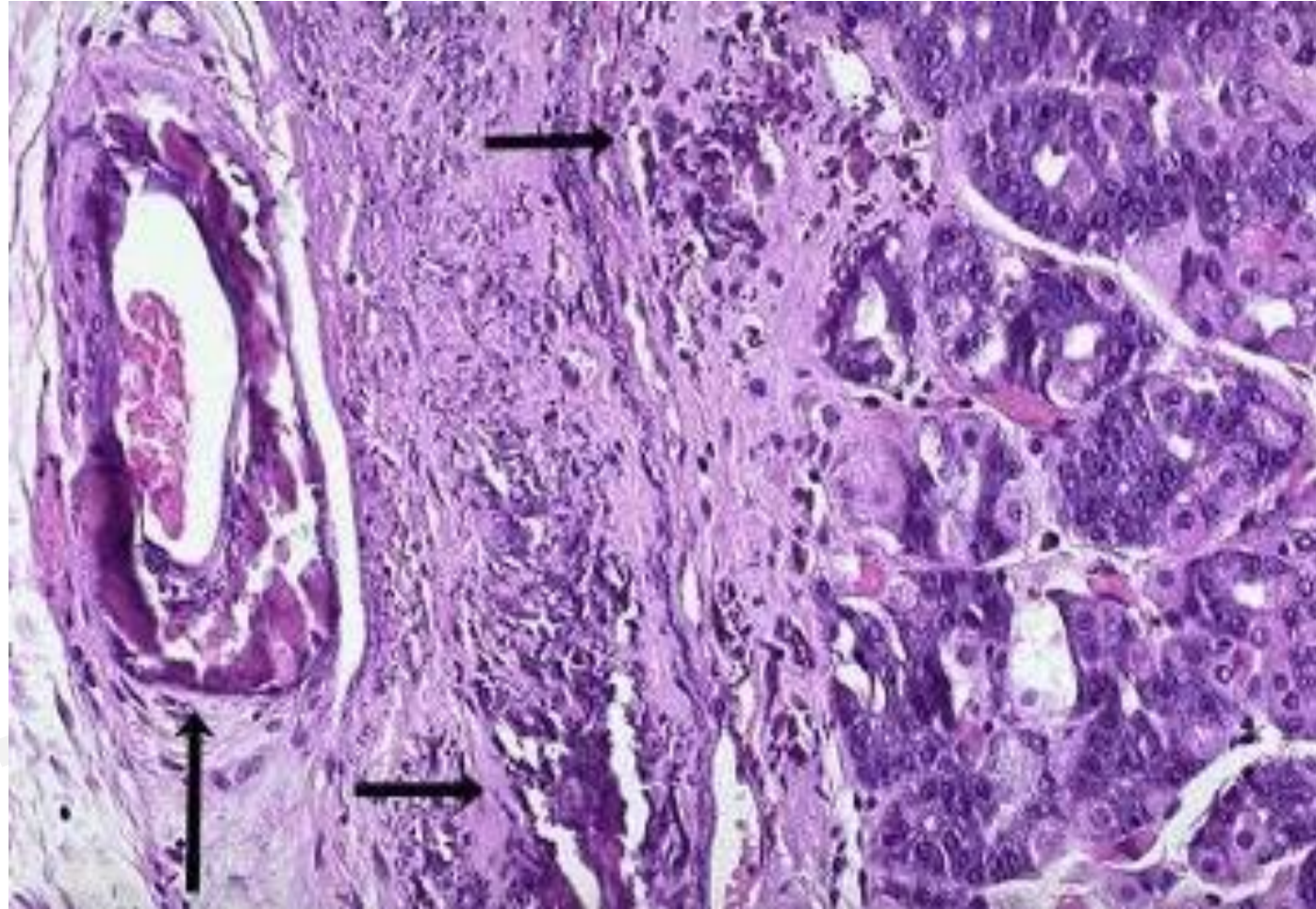
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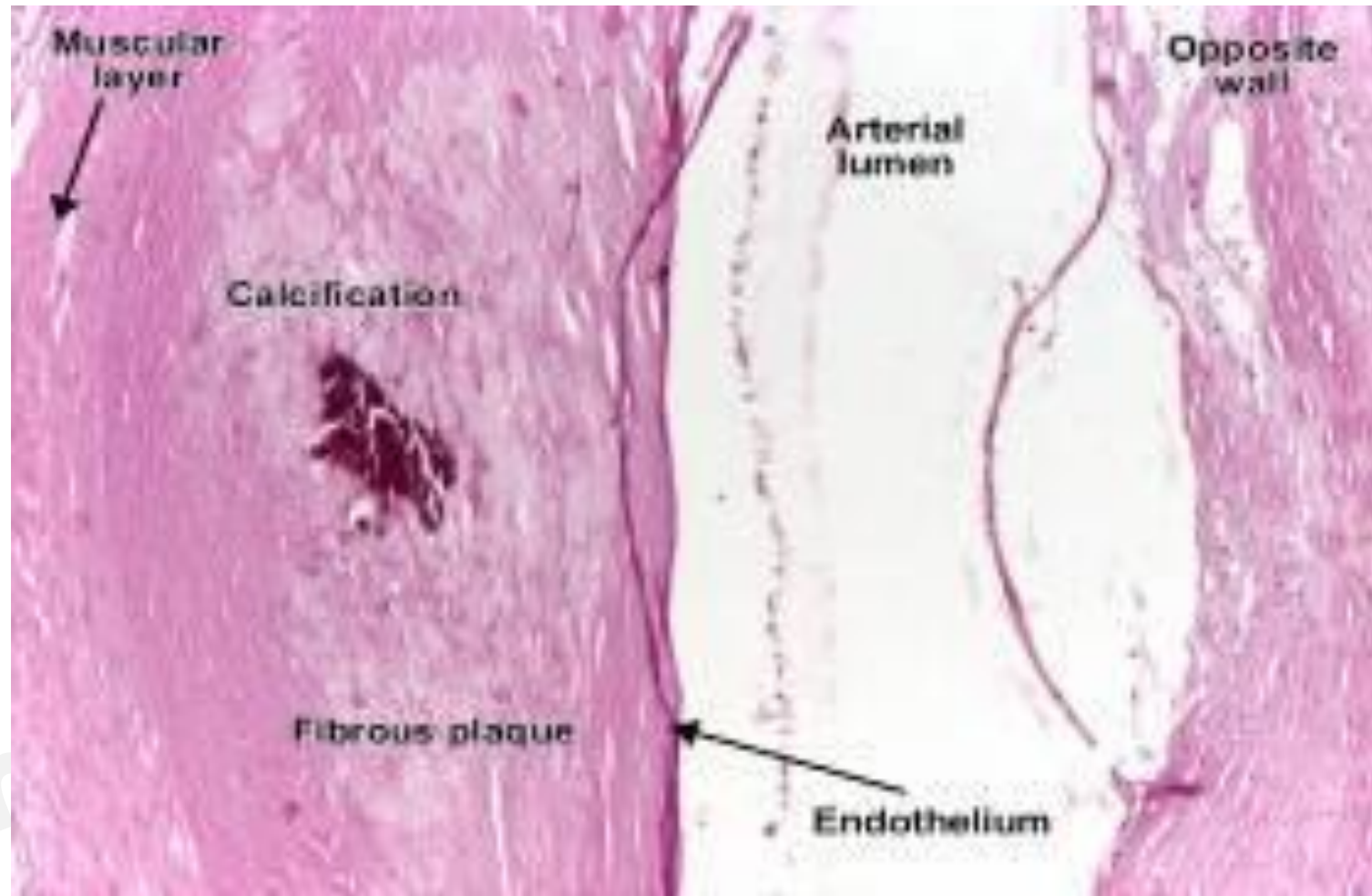


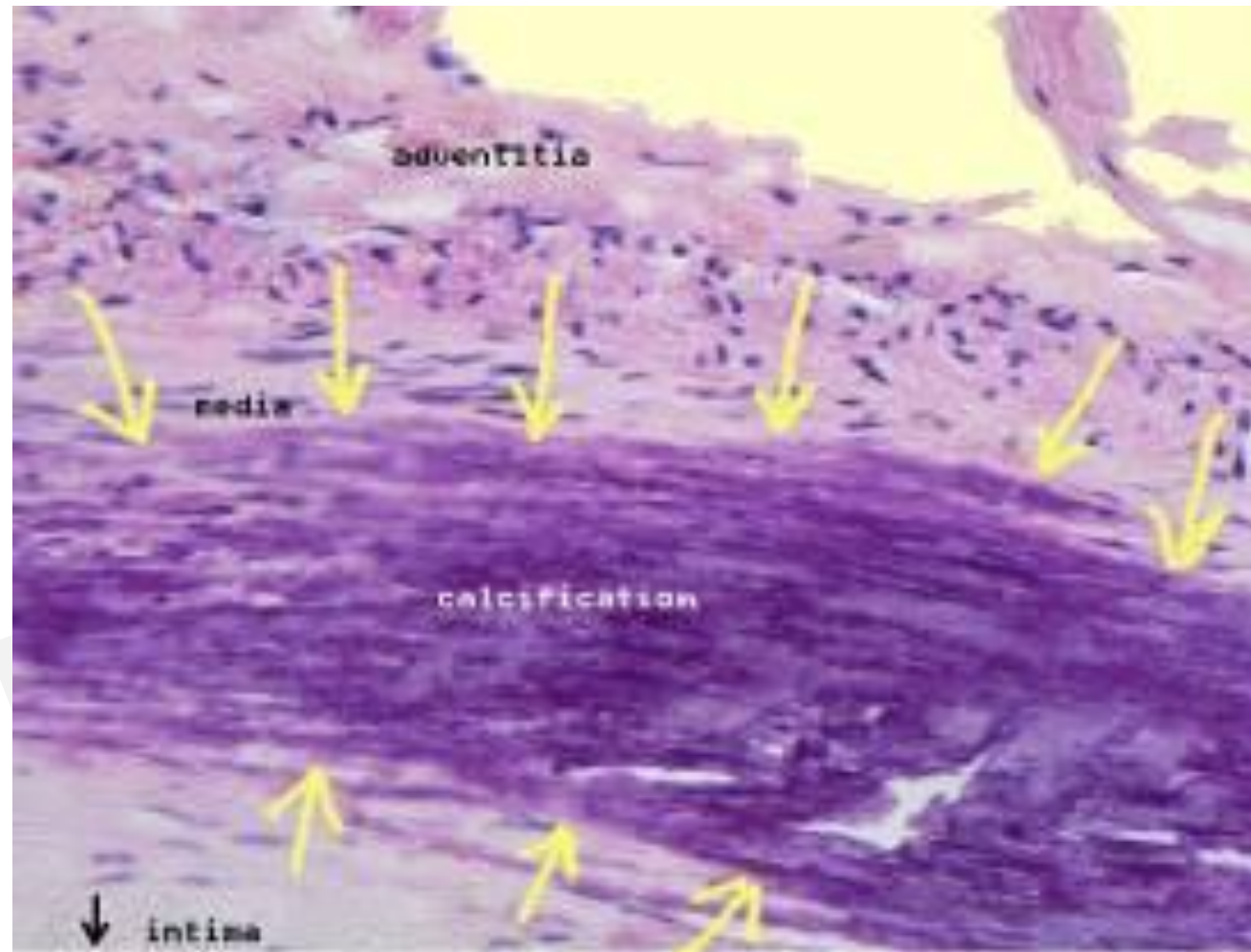
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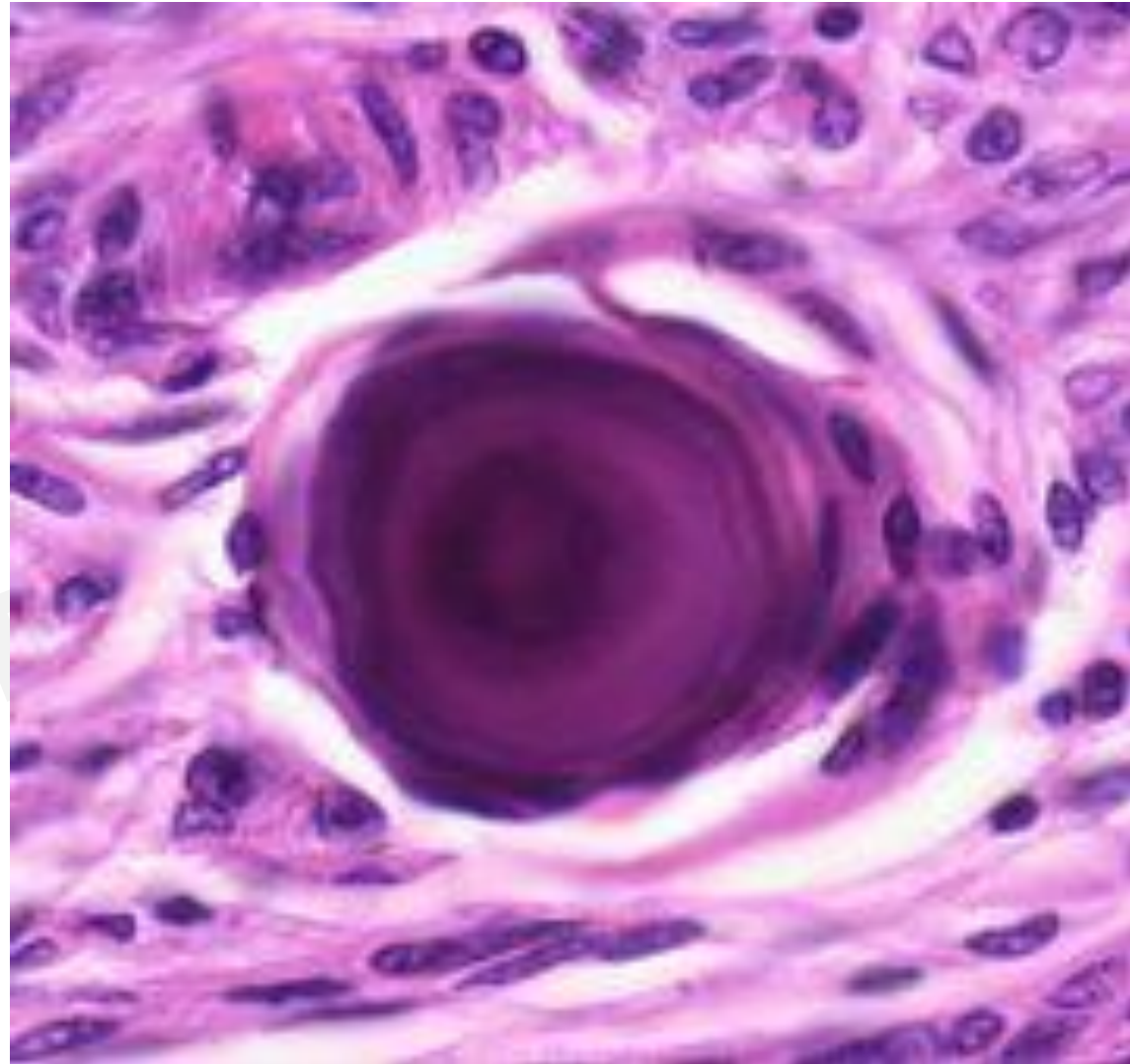
Microscopic appearance:

- Calcium salts appear as **blue granules (deep basophilic) on H& E.**
- Single necrotic cells act like little grains of sand around which a “pearl” of calcium is deposited. This is called a **psammoma body**
- Special stain **Von Kossa** gives a **black** color, **Alizarin red S** that produces **red** staining









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Significance and results

- Calcification is usually **harmless**.
- May cause hindrance to organs motility and **inelasticity**.

Both types of calcification consist of **calcium phosphate crystals**

The big difference is that →

- **Dystrophic calcification** occurs in damaged tissue and normal blood calcium level
- **Metastatic calcification** occurs in normal tissue in the setting of hypercalcemia

FEATURE	DYSTROPHIC CALCIFICATION	METASTATIC CALCIFICATION
1. <i>Definition</i>	Deposits of calcium salts in dead and degenerated tissues	Deposits of calcium salts in normal tissues
2. <i>Calcium metabolism</i>	Normal	Deranged
3. <i>Serum calcium level</i>	Normal	Hypercalcaemia
4. <i>Reversibility</i>	Generally irreversible	Reversible upon correction of metabolic disorder
5. <i>Causes</i>	Necrosis (caseous, liquefactive, fat), infarcts, thrombi, haematomas, dead parasites, old scars, atheromas, Mönckeberg's sclerosis, certain tumours, cysts, calcinosis cutis	Hyperparathyroidism (due to adenoma, hyperplasia, CRF), bony destructive lesions (e.g. myeloma, metastatic carcinoma), prolonged immobilisation, hypervitaminosis D, milk-alkali syndrome, hypercalcaemia of infancy
6. <i>Pathogenesis</i>	Increased binding of phosphates with necrotic and degenerative tissue, which in turn binds to calcium forming calcium phosphate precipitates	Increased precipitates of calcium phosphate due to hypercalcaemia at certain sites e.g. in lungs, stor-

DYSTROPHIC

NORMAL SERUM CALCIUM
DEAD & DYING TISSUES

ATHEROSCLEROSIS

CALCIFIED GRANULOMAS

CALCIFIC AORTIC STENOSIS

BICUSPID AORTIC STENOSIS

EXTRASKELETAL CALCIFICATION

METASTATIC

HYPERCALCEMIC STATES
CALCIFICATION IN NORMAL
TISSUES: LUNG, KIDNEY,
GASTRIC MUCOSA

MULTIPLE MYELOMA
HYPERPARATHYROIDISM
BONE METASTASIS
END-STAGE KIDNEY
SARCOIDOSIS
HYPERVITAMINOSIS D

POLLS 8

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Dystrophic calcification means-

- a) Calcification in destroyed tissue with normal calcium level in blood
- b) \uparrow level of Ca^{++} deposits
- c) Calcification in normal tissue seen in hyperparathyroidism
- d) Calcification in destroyed tissues with hypercalcemia

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A

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Metastatic calcification is characterized by -

- a) Hypercalcemia
- b) Hypocalcemia
- c) Eucalcemia
- d) None of the above

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Dystrophic calcification is seen in -

- a) Milk alkali syndrome
- b) Atheromatous plaque
- c) Hyperparathyroidism
- d) Vitamin A intoxication

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Which of the following is not a common site for metastatic calcification -

- a) Gastric mucosa
- b) Kidney
- c) Parathyroid
- d) Lung

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C

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True about metastatic calcification -

- a) Serum ca level is normal
- b) Occurs in dead/dying tissue
- c) Occurs in damaged heart valves
- d) Calcification starts in mitochondria

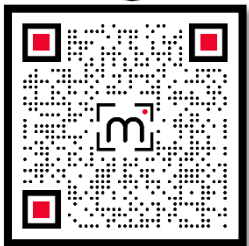
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AGING

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Like us



- Cellular aging is the result of a **progressive decline in cellular function and viability** caused by **genetic abnormalities and the accumulation of cellular damage due to the effects of exposure to exogenous influences**
- Ageing is distinct from mortality and disease although aged individuals are more vulnerable to disease.

- In India, due to improved health care, it has gone up from an average of 26 years at the time of independence in 1947 to 64 years at present.
- Survival is longer in **women than men (3: 2)**.
- The maximum human lifespan has remained stable at about **110 years**.

Life expectancy of an individual depends on

1. Intrinsic genetic process

- the genes controlling response to endogenous and exogenous factors.
- It has been seen that long life runs in families
- high concordance in lifespan of identical twins has been observed.

2. Environmental factors

3. Lifestyle of the individual such as diseases due to alcohol, smoking, drug addiction.

4. Age-related diseases e.g. atherosclerosis and IHD, DM, hypertension, osteoporosis, Alzheimer's disease, Parkinson's disease etc.

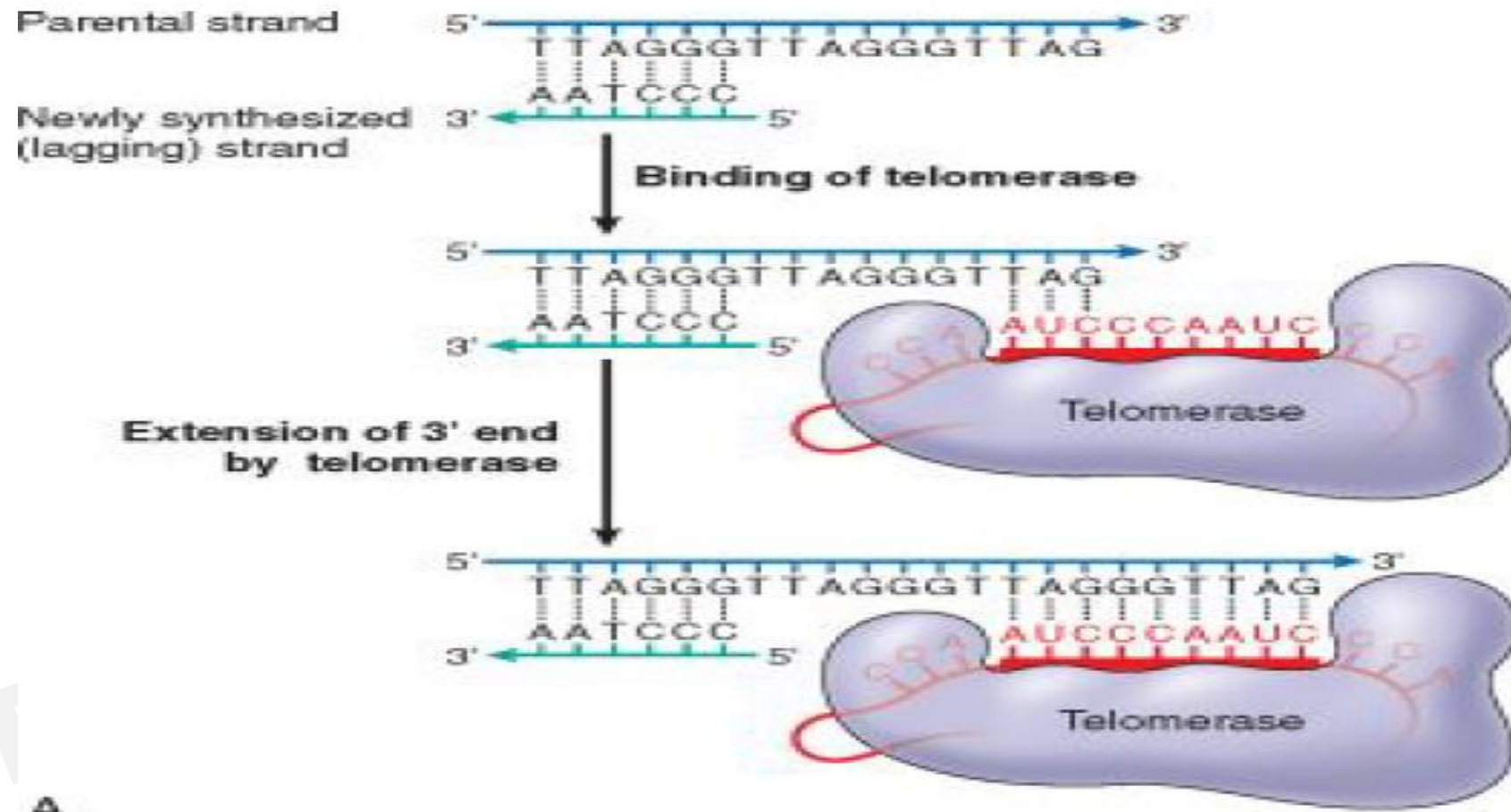
PATHOGENESIS OF AGING

- **1. TELOMERE THEORY**
- **2. Genetic control in invertebrates**
- **3. Diseases of accelerated ageing**
- **4. Oxidative stress hypothesis (free radical-mediated injury)**
- **5. Hormonal decline**
- **6. Defective host defenses**
- **7. Failure to renew**

1. TELOMERE THEORY

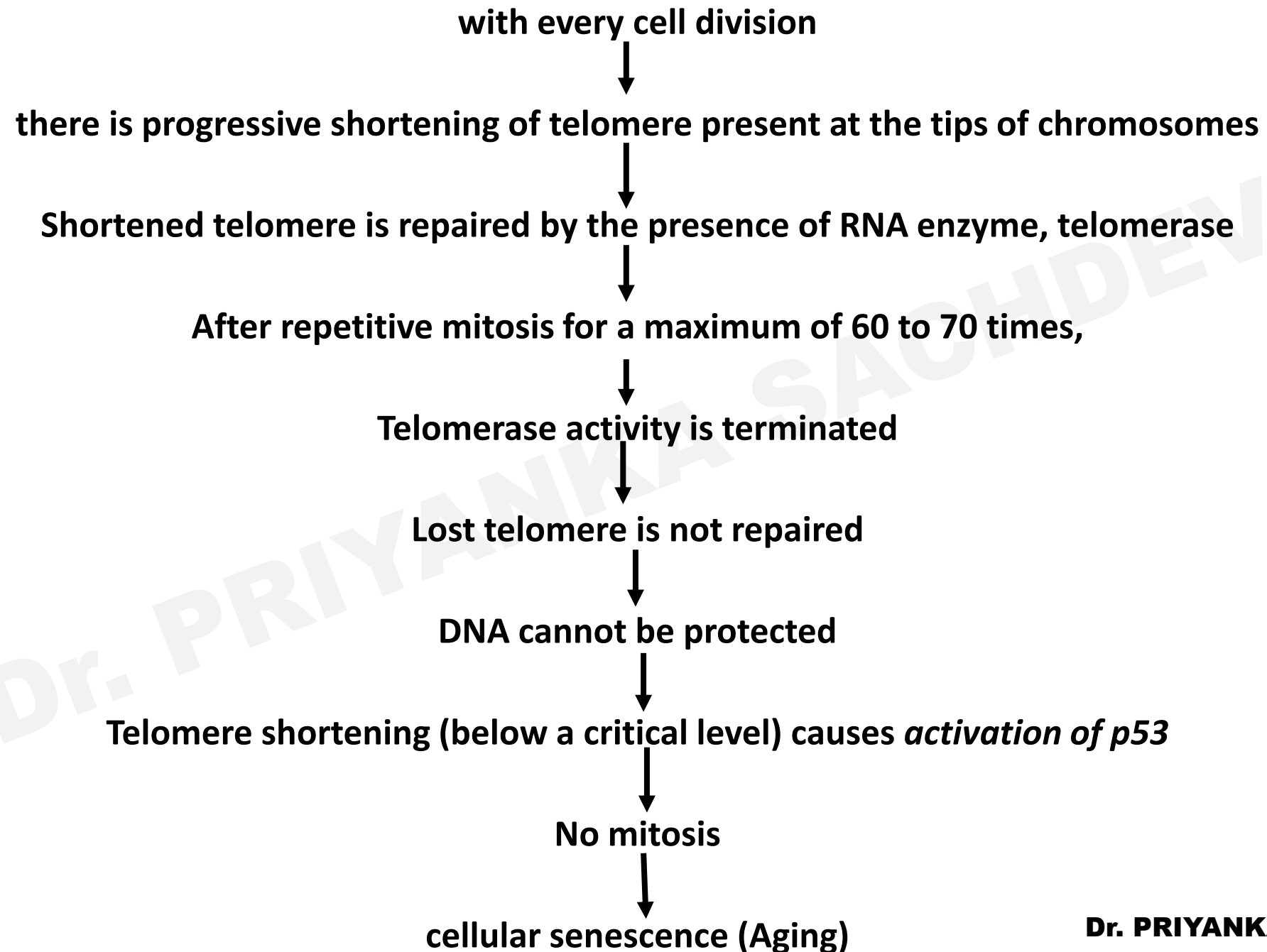
- After a fixed number of divisions all somatic cells become arrested in a terminally nondividing state, known as **senescence**.

- **Telomeres** are short repeated sequences of DNA (TTAGGG) present at the linear ends of chromosomes that are important for protecting DNA
- With every cell division, there is progressive **shortening of telomere** present at the tips of chromosomes
- Telomere length is normally maintained by an enzyme called **telomerase**.
- Telomerase is a specialized RNA-protein complex that uses its own RNA as a template for adding nucleotides to the ends of chromosomes

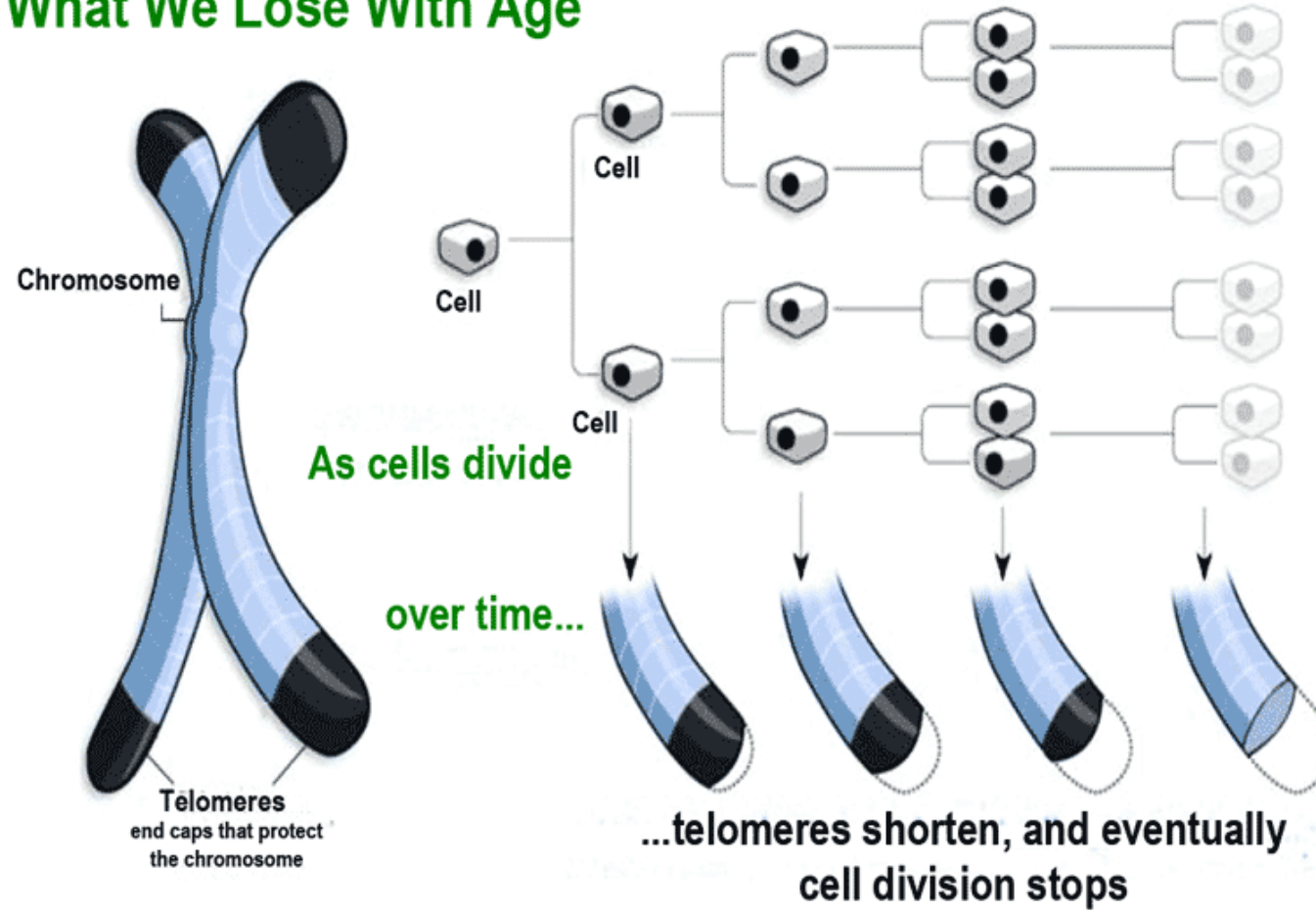


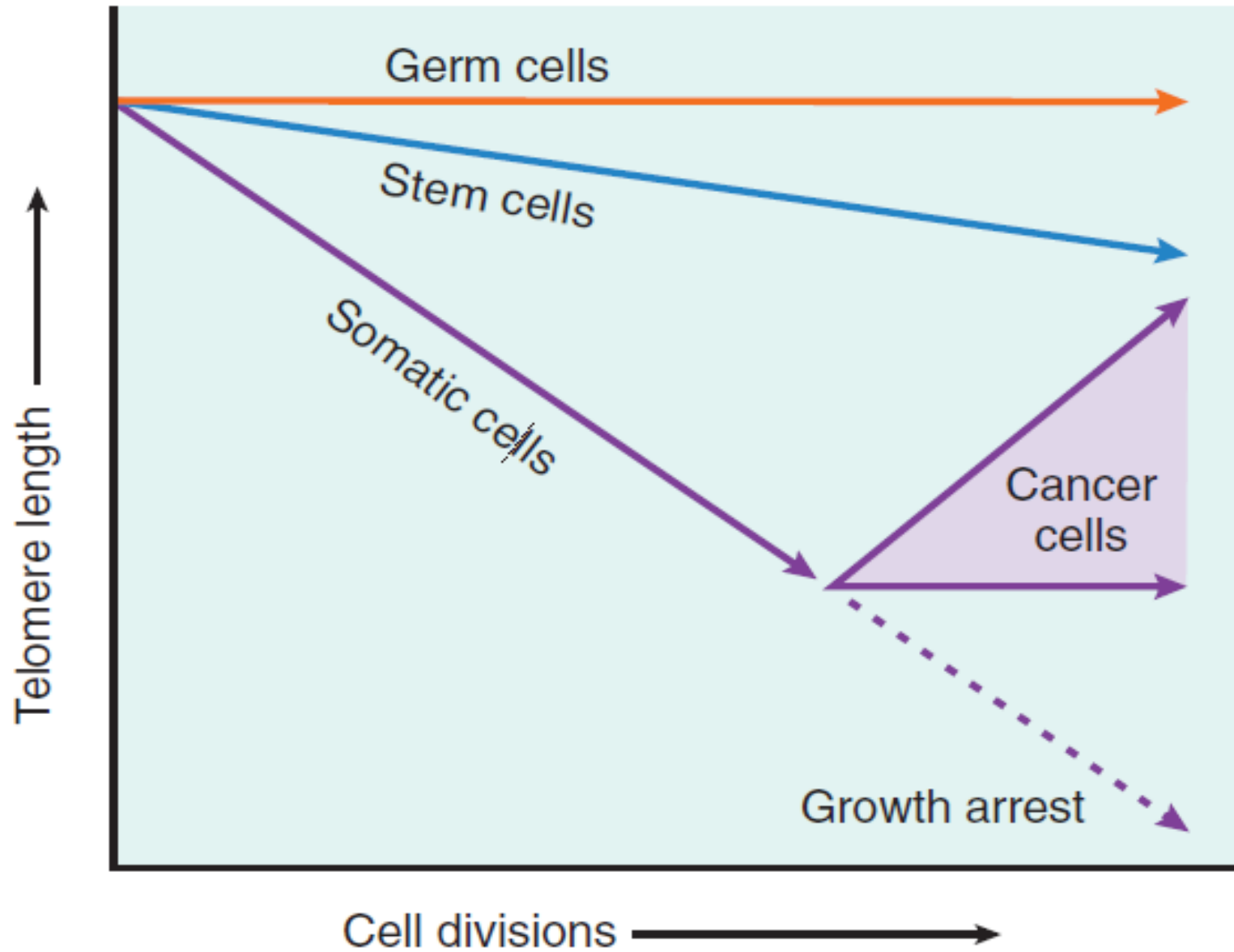
A

- **The activity of telomerase is decreased with age**
- Telomerase activity is highest in germ cells and present at lower levels in stem cells, very low in somatic tissues



What We Lose With Age





2. Genetic control in invertebrates

- **Clock (clk)** genes responsible for controlling the rate and time of ageing identified in lower invertebrates
- e.g. clk-1 gene mutation in the metazoa, results in prolonging the lifespan

3. Diseases of accelerated ageing

- A heritable condition associated with signs of accelerated ageing process known as **progeria**
- **Werner's syndrome**, a rare autosomal recessive disease, characterised by premature ageing
- children is characterised by baldness, cataracts, and coronary artery disease.

4. Oxidative stress hypothesis (free radical-mediated injury)

With ageing, there is generation of toxic oxygen free radicals



Fail to get eliminated



Their accumulation



cell damage

5. Hormonal decline

- With age, there is loss of secretion of some hormones resulting in their functional decline.

6. Defective host defenses

- Ageing causes impaired immune function
- reduced ability to respond to microbes

7. Failure to renew

- Ageing causes accumulation of senescent cells without corresponding renewal of lost cells.

PATHOGENESIS OF AGING

- **1. TELOMERE THEORY**
- **2. Genetic control in invertebrates**
- **3. Diseases of accelerated ageing**
- **4. Oxidative stress hypothesis (free radical-mediated injury)**
- **5. Hormonal decline**
- **6. Defective host defenses**
- **7. Failure to renew**

A) Cellular changes :

- Decrease in cell size and number (B/MS 01)
- Decreased in size and number of mitochondria (AI 97)
- Detachment of ribosomes from ER
- Increased number of phagolysosomal vacuoles
- Defective DNA repair
- Non-enzymatic glycosylation of protien (AI 97)

B) Connective tissue changes :

- There is loss of elasticity (wrinkling of skin)
- ↑ BP due to decreased elasticity of artery
- Ground glass substance changes (cataract)
- Cartilage and bone changes (osteoarthritis, osteoporosis)

C) Decreased immunity :

- Decreased T cells, B cells, plasma cells and antibodies.

ORGAN CHANGES IN AGEING

- 1. Cardiovascular system:** Atherosclerosis, arteriosclerosis with calcification, Mönckeberg's medial calcification, brown atrophy of the heart
- 2. Nervous system:** Atrophy of gyri and sulci, Alzheimer's disease, Parkinson's disease.
- 3. Musculoskeletal system:** Degenerative bone diseases, frequent fractures, muscular degeneration

- 4. Eyes:** Deterioration of vision due to cataract and vascular changes in retina.
- 5. Hearing:** Disability in hearing due to senility is related to otosclerosis.
- 6. Immune system:** Reduced IgG response to antigens
- 7. Skin:** Laxity of skin due to loss of elastic tissue.
- 8. Cancers:** 80% of cancers occur in the age range of 50-80 years.

POLLS ?????

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Inflammation*



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Which of the following is associated with aging -

- a) Reduced cross linkages in collagen
- b) Increased free radical injury
- c) Decreased Somatic mutations in DNA
- d) Increased superoxide dismutase levels

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B

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All of the following statements are true for cell aging except -

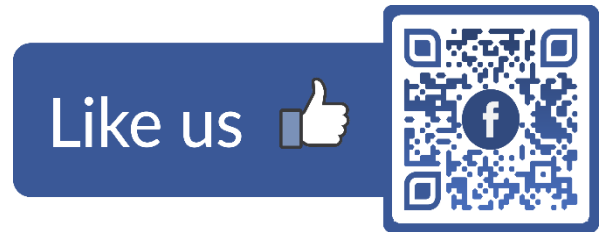
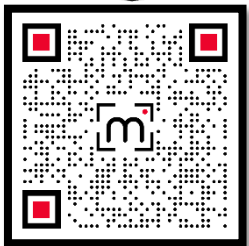
- a) Enlargement of telomere
- b) Decrease number of mitochondria
- c) Glycolysation of DNA
- d) Glycolysation of RNA

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Thank you for being awake



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NEXT CLASS

- Every **MWF** (Monday , Wednesday , Friday)→**PATHOLOGY**
- Every **TTS** (Tuesday , Thursday , Saturday) →**PHARMACOLOGY**

FREE LIVE CLASSES

COMPLETE

PHARMACOLOGY

By Dr Priyanka Sachdev

10 Nov - Pharmacokinetics part 1
17 Nov - Pharmacokinetics part 2
19 Nov - Pharmacodynamics
21 Nov - ANS part 1
24 Nov - ANS part 2
26 Nov - ANS part 3
28 Nov - Drugs for Asthma
01 Dec - Oral Hypoglycaemic Agents and Insulin
03 Dec - CNS - Sedatives and hypnotics, Alcohol
05 Dec - CNS - Anti Parkinson's drug
08 Dec - Drugs affecting RAS
10 Dec - Anti-angina and Heart failure drugs
12 Dec - Diuretics, Antidiuretics
15 Dec - Antimicrobials part 1
17 Dec - Antimicrobials part 2

EVERY TTS
4 - 6 PM

FREE LIVE CLASSES

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PATHOLOGY

By Dr Priyanka Sachdev

11 Nov - Cell Adaptation and injury
16 Nov - Inflammation
18 Nov - Hemodynamics
20 Nov - Neoplasia part 1
23 Nov - Neoplasia part 2
25 Nov - Disorders of RBC 1
27 Nov - Disorders of RBC 2
02 Dec - Disorders of WBC
04 Dec - Disorders of platelets
07 Dec - Cardiovascular system
09 Dec - Respiratory system
11 Dec - GIT / Liver
14 Dec - Renal system
16 Dec - Practical and Viva voce (2nd Prof)

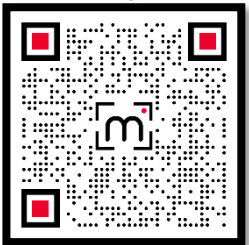
EVERY MWF
4 - 6 PM

TOMORROW

• 17th Nov → Tuesday → PHARMACOLOGY

PHARMACOKINETICS (Part 2)

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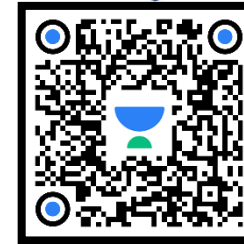
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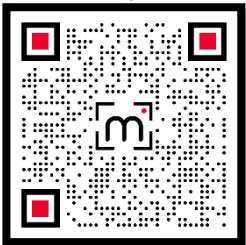


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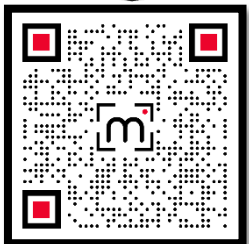
THANK YOU



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